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CASE REPORT

Development of IgA vasculitis with severe glomerulonephritis after COVID-19 vaccination: a case report and literature review

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Abstract

With the worldwide spread of the COVID-19 vaccine program during the COVID-19 pandemic, the numbers of reported cases with new-onset or relapsed kidney disease/vasculitis such as minimal change nephrotic syndrome, immunoglobulinA (IgA) nephropathy, and IgA vasculitis (IgAV) that developed after COVID-19 vaccination are increasing. We present the case of a 67-year-old Japanese woman who developed IgAV with purpura on her extremities and trunk in the evening of the day that she received the second dose of the Pfizer-BioNTech COVID-19 vaccine. She subsequently presented with acute kidney injury and nephrotic syndrome, and a kidney biopsy performed 14 days after the second vaccination showed diffuse mesangial and endocapillary glomerulonephritis with necrotizing crescent formation, accompanied by IgA deposition. One steroid pulse plus four administrations of a monthly intravenous cyclophosphamide injection were applied, followed by oral azathioprine during oral steroid tapering. Her response to this treatment was unsatisfactory and intractable for some time. Eventually, her renal function improved and nephrotic syndrome was resolved, while microscopic hematuria and proteinuria at ~ 1 g/gCr remained at 6 months post-vaccination. Unlike the previous milder renal-involved IgAV cases following COVID-19 vaccination, our patient's case presented severe glomerulonephritis and took a long time to recover despite intensive initial immunosuppressive treatment.

Keywords IgA vasculitis · IgAV · Glomerulonephritis · COVID-19 vaccination

Introduction

ImmunoglobulinA (IgA) vasculitis (IgAV) is an immune-complex mediated systemic vasculitis associated with IgA. The underlying cause of IgAV is unknown, but immunological, genetic, and environmental factors are all thought to be involved [1–3]. IgAV is known to be triggered by an activation of the immune system by infection and by a variety of chemicals [1–3]. There are some reports of IgAV that developed after measles-mumps-rubella (MMR) vaccination or influenza vaccination [4–6]. With the spread of the COVID-19 pandemic and the COVID-19 vaccine programs worldwide, new-onset and relapses of primary kidney disease/vasculitis with kidney involvement that developed after COVID-19 vaccination have recently been reported [7–12]. The association between hematuria following a COVID-19 vaccination with the onset or relapse of IgA nephropathy [13] has been attracting attention, and reports of IgAV (Henoch-Schönlein purpura with/without kidney complication) after COVID-19 vaccination are also increasing in number [14–22].

Here, we present the case of a patient who exhibited IgAV immediately after receiving the second dose of a COVID-19 vaccine. Although the renal complications of all past IgAV cases were mild [14–22], our patient developed severe glomerulonephritis, and it took a considerable amount of time for her recovery despite intensive initial immunosuppressive treatment.

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Case report

A 67-year-old Japanese woman with a history of hypertension developed an erythematous maculopapular rash on her left leg in the evening of the same day that she received the second dose of the Pfizer-BioNTech COVID-19 vaccine by intramuscular injection. She had undergone regular medical checkups, and she had no history of urinary abnormalities or purpura in the past. She had received the first dose of the same vaccine 3 weeks prior. At approx. 5 h after the patient was administered her second vaccination, the rash had spread to both legs, upper limbs, and hips, with subcutaneous edema. The day after the second vaccination, the patient first noticed gross hematuria. On day seven after the second vaccination, the patient visited the department of internal medicine at our hospital and was examined at the department of nephrology. She was admitted to the department of nephrology on day 12.

On her admission, she showed renal impairment with serum creatinine (sCr) at 0.83 mg/dl, the estimated glomerular filtration rate (eGFR) 52.6 ml/min/1.73m^2, urine protein (3 +), protein quantification 5.1 g/gCr, urine occult blood (3 +), and urine sediment of red blood cells > 100/HPF (high-power fields). The results of tests for antineutrophil cytoplasmic antibody (ANCA) and cryoglobulins were negative, all other autoantibodies were negative, complement was within normal range, and IgA was within the reference range.

A kidney biopsy was performed on day 14, and a skin biopsy was performed on day 15, after which methylprednisolone 500 mg was administered intravenously for 3 days, followed by daily prednisolone 40 mg (0.8 mg/kg). After the initiation of the steroid, the patient's purpura, arthritis, and abdominal pain improved, but leg edema remained. In the specimens from the kidney biopsy, all 36 glomeruli showed mesangial or endocapillary proliferative changes (Fig. 1a, b), 15 of which were accompanied by necrotizing cellular crescent formation (Fig. 1c). All necrotizing cellular crescents lesions were similar, suggesting that these lesions had developed within the same time period, i.e., at the acute phase. There was no tubulointerstitial damage.

Immunofluorescent staining on a frozen section showed IgA and C3 deposition in the mesangial areas (Fig. 2). An electron microscopy examination revealed cell proliferative changes with an electron-dense deposit in the mesangial area. The foot process effacement of podocytes was limited to sites with endocapillary proliferative changes (Fig. 3). A skin biopsy showed leukocytoclastic vasculitis, suggesting small-vessel vasculitis. The patient's renal function worsened to the maximum sCr value of 2.2 mg/dl with the eGFR 18.1 ml/min/1.73m^2, accompanied by nephrotic-range massive proteinuria; her hypoalbuminemia was minimally 2.1 g/dL.

Since the patient's nephritis with nephrotic-range proteinuria continued for 4 weeks, we started monthly intravenous cyclophosphamide (IVCY) 500 mg. The monthly IVCY was performed four times. At 4 months after the initiation of the IVCY treatment, the patient's urinary protein had decreased to 1 g/gCr and her leg edema was also improved. The IVCY was discontinued and switched to oral azathioprine. The oral glucocorticoid (prednisolone) during tapering was reduced to 10 mg/day at that point.

6 months after the start of the patient's treatment, her renal function was improved at sCr 0.65 mg/dl and eGFR 68.7 ml/min/1.73m^2, but the urinary protein value continued to be around 1 g/gCr, and the microscopic hematuria also continued.

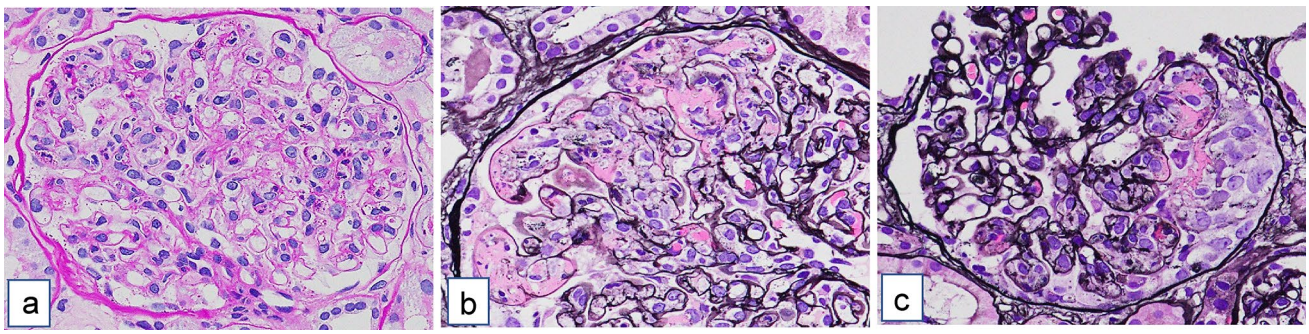

Fig. 1 **a** A glomerulus showing mesangial- and endocapillary-proliferative changes. Periodic acid Schiff staining, ×200. **b** Endocapillary proliferative changes with mesangiolysis are observed from 9 o'clock to 12 o'clock in a glomerulus. Periodic acid-methenamine-silver ×200. **c** With endocapillary proliferative lesions, tuft necrosis with a cellular crescent formation is observed from 2 o'clock to 6 o'clock in a glomerulus. Periodic acid-methenamine-silver, ×200

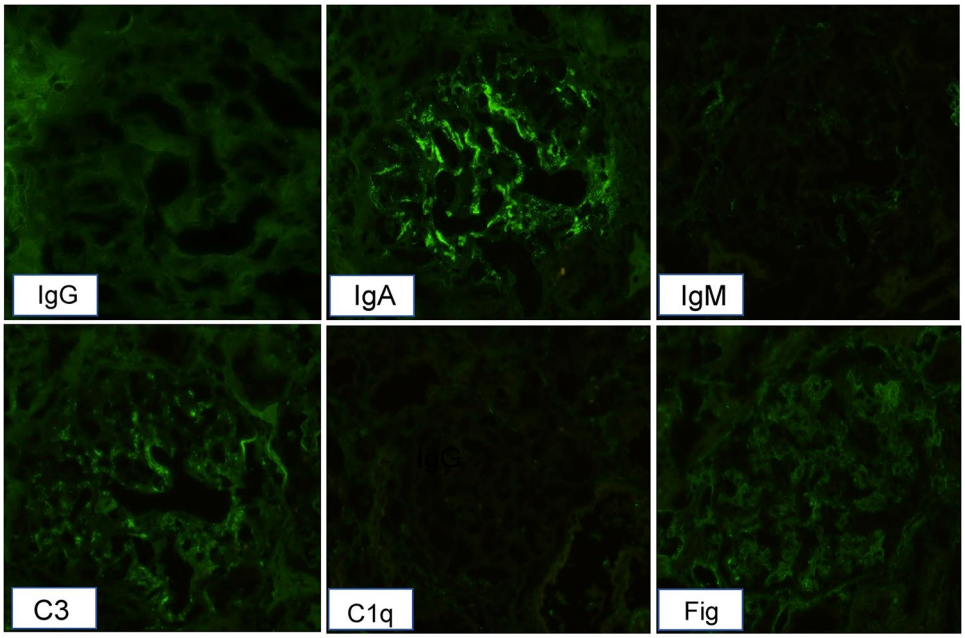

Fig. 2 Immunofluorescent staining on a frozen section. Anti-IgA staining was positive in mesangial areas. Anti-C3 staining was weakly positive in mesangial areas. Anti-IgG, IgM, C1q, and fibrinogen were negative

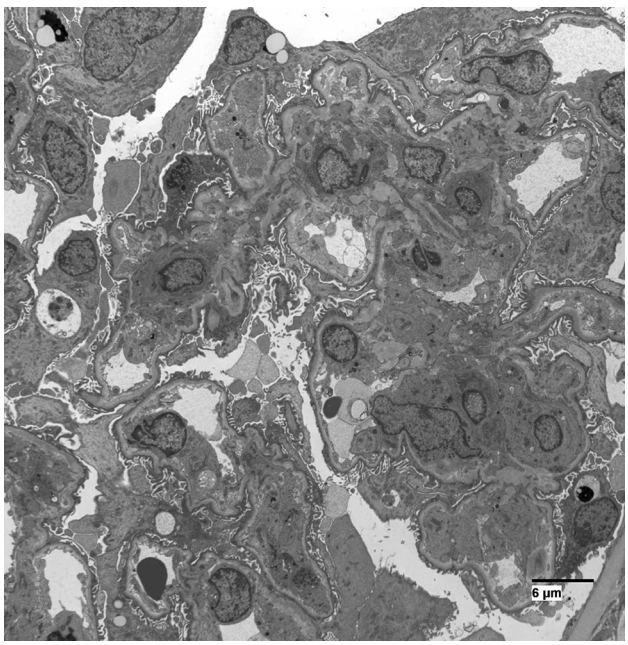

Fig. 3 An electron microscopic observation of a glomerulus. Cell proliferations are partially present in the mesangial areas and the capillary lumens. The electron-dense deposits are scattered in the mesangial areas. The foot-process effacement of podocytes is limited to the loops of the cell-proliferative portion. The reference length is shown at the lower right

Discussion

As mentioned above, the numbers of reported cases with new-onset or relapsed IgA nephropathy and IgAV that developed after COVID-19 vaccination are increasing. Although no clear conclusions can be drawn, there are some reports on the association of the development of IgAV after vaccination [4–6, 23].

An increased risk of IgAV within 12 weeks after measles-mumps-rubella vaccination was reported (odds ratio [OR] 3.4, 95% CI: 1.2–10.0), which was not seen with other vaccines [5]. In contrast, in a case-crossover study of various vaccines in 167 children, the risk of IgAV within 3 months after vaccination was not increased compared with the 3 months before vaccination (OR 1.6, 95% CI: 0.8–3.0) [4]. The messenger RNA (mRNA) vaccines for SARS-COv-2 such as those produced by Pfizer-BioNTech and Moderna have a pioneer mechanism of action that produces the spike proteins as viral antigens in target cells of the host. Nucleoside-modified mRNA wrapped in a lipid nanoparticle encodes the SARS-CoV-2 spike protein and releases it into the cytoplasm of target cells of the host, where it is translated by ribosomes to produce viral antigens, which are presented on the surface of Th1 cells and trigger immune responses such as the activation of killer T cells, NK cells, macrophages, or B cells to induce antibody production.

The leading immunoglobulin against COVID-19 infection is IgA [24], which provides mucosal immunity. After COVID-19 vaccination, both IgG and IgA are elevated, but their blood kinetics are different, with IgG lasting longer [25]. Obeid et al. reported a case of relapsed IgAV following Moderna vaccination. They observed a specific increase of anti-spike IgA antibodies after COVID-19 vaccination in the patient's serum. They also reported that the patient had a transient IgA-type antinuclear antibody after vaccination, and this disappeared with steroid treatment [14].

Table 1 A summary of previous IgAV cases after COVID-19 vaccination

First author, country and ref. no	Age, yrs	Sex	Time to presentation from vaccination	Vaccine dose	Vaccine brand	New onset or relapse	sCr(mg/dL) at development eGFR development to maximum	Proteinuria	Hematuria	Renal biopsy	Initial dose of steroid treatment	Renal outcome
Obeid, Switzerland [12]	78	F	7 days	1	Moderna	relapse	1.18	NA	150×106/L	NA	mPSL1g pulse	NA impoved rapidly
Maye,UK [13]	23	M	< 24 h	2	Pfizer-BioNTech	relapse	eGFR79, sCr112μmol	4.9 mg/mmol (alb/cr)	165/mm3	NA	OGC 20 mg	CR
Badier, France [14]	72	M	15 days	1	Oxford-Astra-Zeneca	new onset	NA	NA	NA	NA	OGC 20 mg	CR
Grossman, USA [15]	94	M	10 days	2	Moderna	new onset	1.2→2.4 mg/dL	3+	3+	NA	OGC 60 mg	toward normal within several months
Iwata, Japan [16]	70	F	2 days	2	Pfizer-BioNTech	new onset				NA hemodialysis 10yrs prior	observation	
Hines, USA [17]	40	F	20 days	1	Pfizer–BioNTech	new onset	normal		2/HPF	NA	observation	NA
Mohamed, Australia [18]	50	M	14 days	1	Pfizer–BioNTech	new onset				NA	OGC 60 mg for skin	UP 0.5 g/d for on day100
			skin: 2 days, kidney: 3 weeks	2		relapse	0.9 mg/dL	1.1 g/d	10/HPF	mild mesangial hypercellularity 1 of the 16 glomeruli	ACEi	
Sirufo, Italy [19]	76	F	7 days	1	Oxford-Astra-Zeneca	new onset	0.7 mg/dL	negative	72/HPF	NA	Acetaminophen, Deflazacort	CR in 6 weeks
Wang, Singapore [20]	15	F	2 h	2	Pfizer-BioNTech	new onset	NA	positive	18/μL	NA	90 mg ertocoxib and topical betamethasone valerate 0.1% cream	NA
Naitlho, Morocco [21]	62	M	8 days	1	Oxford-Astra-Zeneca	new onset	NA	NA	200/mL	NA	OGC 40 mg	NA
Bostan, Turkey [22]	33	M	3 days	1	mRNA vaccine (unknown)	new onset	NA	NA	NA	NA	Topical mometasone furoate	NA

ACEi angiotensin-converting enzyme inhibitor, *CR* complete remission, *eGFR* estimated glomerular filtration rate, *F* female, *HPF* high power field, *M* male, *mPSL* methylprednisolone, *NA* not available, *OGC* oral glucocorticoid, *sCr* serum creatinine, *yrs* years

Table 1 summarizes the cases of IgAV after vaccination that we found using a search of the Pubmed and Google Scholar databases as of January 27, 2022. The time to IgAV onset after vaccination ranged from 2 h to 20 days [14–22]. Urinary findings suggesting nephritis were mild and transient, and only one biopsy-proven case with mild glomerulonephritis was reported [20]. The period of IgA elevation after COVID-19 vaccination is transient and shorter [24, 25], and the onsets of IgAN and IgAV after vaccination are earlier than that of minimal change of nephrotic syndrome [12], suggesting that these onsets occur during IgA elevation. All acute-phase lesions in the present case seemed to be a simultaneous development, which suggests that the onset was very limited to a short period after the vaccination. However, we did not investigate the time course of the patient's serum IgA levels.

The clinical course of glomerulonephritis in our patient's case was severe, refractory, and persistent despite intensive immunosuppressive treatment. Whether post-vaccination IgAV is complicated by glomerulonephritis or recovers without nephritis is an important point to discuss. This is an argument similar to the difference in mechanisms between severe/persistent and mild/transient cases of IgAV-glomerulonephritis, which has not been fully elucidated. Suzuki et al. showed that IgAV patients with nephritis had higher production and circulation of galactose-deficient (GD)IgA1 and GD IgA1-specific IgG autoantibodies compared to healthy subjects and IgAV patients without nephritis [26]. That report's findings indicate that it is possible that our present patient had large amounts of galactose-deficient (GD) IgA1 and GDIgA1-specific IgG autoantibodies that were necessary to develop and maintain severe nephritis. Unfortunately, neither GD-IgA1 nor GD-IgA1-specific IgG was examined in her case.

The adverse effects of COVID-19 vaccine have been generally accepted to date. Despite the unprecedented frequency of the vaccines' use for adults worldwide, the reports of IgAV after COVID-19 vaccine are not frequent and the clinical prognoses are mild and transient in almost all cases. However, experts should be aware that some cases can progress to severe glomerulonephritis.

IgAV is a systemic vasculitis that predominantly affects children between the ages of 3 and 15 years.[1–3] In Japan at this time, the pros and cons of vaccinating infants and school children are under consideration. If COVID-19 vaccination becomes more widespread among young people in the future, the number of cases of IgAV (including severe forms) can be expected to increase, and thus epidemiological surveys as well as a clarification of the mechanisms of development are needed.

Declarations

Conflict of interest All the authors have declared no competing interest.

Consent for publication Fully informed written consent for the publication of her case was obtained from the patient.

References

1. Rigante D, Castellazzi L, Bosco A, Esposito S. Is there a crossroad between infections, genetics, and Henoch-Schönlein purpura? Autoimmun Rev. 2013;12:1016.
2. Yang YH, Yu HH, Chiang BL. The diagnosis and classification of Henoch-Schönlein purpura: an updated review. Autoimmun Rev. 2014;13:355.
3. Trnka P. Henoch-Schönlein purpura in children. J Paediatr Child Health. 2013;49:995–1003.
4. Piram M, Gonzalez Chiappe S, Madhi F, Ulinski T, Mahr A. Vaccination and risk of childhood IgA vasculitis. Pediatrics. 2018;142:e20180841.
5. Da Dalt L, Zerbinati C, Strafella MS, Renna S, Riceputi L, Di Pietro P, Barabino P, Scanferla S, Raucci U, Mores N, Compagnone A, Da Cas R, Menniti-Ippolito F. Italian multicenter study group for drug and vaccine safety in children. Henoch-Schönlein purpura and drug and vaccine use in childhood: a case-control study. Ital J Pediatr. 2016;42:60.
6. Watanabe T. Vasculitis following influenza vaccination: a review of the literature. Curr Rheumatol Rev. 2017;13:188–96.
7. Shakoor MT, Birkenbach MP, Lynch M. ANCA-associated vasculitis following Pfizer-BioNTech COVID-19 vaccine. Am J Kidney Dis. 2021;78:611–3.
8. Hanna J, Ingram A, Shao T. Minimal change disease after first dose of Pfizer-BioNTech COVID-19 vaccine: a case report and review of minimal change disease related to COVID-19 vaccine. Can J Kidney Health Dis. 2021;8:20543581211058270.
9. Klomjit N, Alexander MP, Fervenza FC, Zoghby Z, Garg A, Hogan MC, Nasr SH, Minshar MA, Zand L. COVID-19 Vaccination and glomerulonephritis. Kidney Int Rep. 2021;6:2969–78.
10. Sacker A, Kung V, Andeen N. Anti-GBM nephritis with mesangial IgA deposits after SARS-CoV-2 mRNA vaccination. Kidney Int. 2021;100:471–2.
11. Abramson M, Mon-Wei YuS, Campbell KN, Chung M, Salem F. IgA Nephropathy after SARS-CoV-2 vaccination. Kidney Med. 2021;3:860–3.
12. Wu HHL, Kalra PA, Chinnadurai R. New-onset and relapsed kidney histopathology following COVID-19 vaccination: a systematic review. Vaccines (Basel). 2021;9:1252.
13. Farooq H, Aemaz Ur Rehman M, Asmar A, Asif S, Mushtaq A, Qureshi MA. The pathogenesis of COVID-19-induced IgA nephropathy and IgA vasculitis: a systematic review. J Taibah Univ Med Sci. 2022;17:1–13.
14. Obeid M, Fenwick C, Pantaleo G. Reactivation of IgA vasculitis after COVID-19 vaccination. Lancet Rheumatol. 2021;3:e617.
15. Maye JA, Chong HP, Rajagopal V, Petchey W. Reactivation of IgA vasculitis following COVID-19 vaccination. BMJ Case Rep. 2021;14:e247188.
16. Badier L, Toledano A, Porel T, Dumond S, Jouglen J, Sailler L, Bagheri H, Moulis G, Lafaurie M. IgA vasculitis in adult patient following vaccination by ChadOx1 nCoV-19. Autoimmun Rev. 2021;20:102951.

17. Grossman ME, Appel G, Little AJ, Ko CJ. Post-COVID-19 vaccination IgA vasculitis in an adult. J Cutan Pathol. 2021. https://doi.org/10.1111/cup.14168.
18. Iwata H, Kamiya K, Kado S, Nakaya T, Kawata H, Komine M, Ohtsuki M. Case of immunoglobulin a vasculitis following coronavirus disease 2019 vaccination. J Dermatol. 2021;48:e598–9.
19. Hines AM, Murphy N, Mullin C, Barillas J, Barrientos JC. Henoch-Schönlein purpura presenting post COVID-19 vaccination. Vaccine. 2021;39:4571–2.
20. Mohamed MMB, Wickman TJ, Fogo AB, Velez JCQ. De novo immunoglobulin a vasculitis following exposure to SARS-CoV-2 immunization. Ochsner J. 2021;21:395–401.
21. Sirufo MM, Raggiunti M, Magnanimi LM, Ginaldi L, De Martinis M. Henoch-Schönlein purpura following the first dose of COVID-19 viral vector vaccine: a case report. Vaccines (Basel). 2021;9:1078.
22. Bostan E, Gulseren D, Gokoz O. New-onset leukocytoclastic vasculitis after COVID-19 vaccine. Int J Dermatol. 2021;60:1305–6.
23. McNally A, McGregor D, Searle M, Irvine J, Cross N. Henoch-Schönlein purpura in a renal transplant recipient with prior IgA nephropathy following influenza vaccination. Clin Kidney J. 2013;6:313–5.
24. Bruel T, Schwartz O, Lacorte JM, Yssel H, Parizot C, Dorgham K, Charneau P, Amoura Z, Gorochov G. IgA dominates the early neutralizing antibody response to SARS-CoV-2. Sci Transl Med. 2021;13:eabd2223.
25. Wisnewski AV, Campillo Luna J, Redlich CA. Human IgG and IgA responses to COVID-19 mRNA vaccines. PLoS ONE. 2021;16:e0249499.
26. Suzuki H, Moldoveanu Z, Julian BA, Wyatt RJ, Novak J. Autoantibodies specific for galactose-deficient IgA1 in IgA vasculitis with nephritis. Kidney Int Rep. 2019;4:1717–24.