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IgA Vasculitis Following COVID-19 Vaccination: A French Multicenter Case Series Including 12 Patients

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ABSTRACT. ***Objective.*** The worldwide coronavirus disease 2019 (COVID-19) vaccination campaign triggered several autoimmune diseases. We hereby aimed to describe IgA vasculitis (IgAV) following COVID-19 vaccination.

Methods. We conducted a national, multicenter, retrospective study in France of new-onset adult IgAV diagnosis following COVID-19 vaccination.

Results. In total, 12 patients with new-onset IgAV were included. Of these, 5 (41.7%) were women, and the median age was 52.5 (IQR 30.75-60.5) years. Of the 12 patients, 10 had received an mRNA vaccine and 2 had received a viral vector vaccine. The median time from vaccination to onset of symptoms was 11.5 (IQR 4.25-21.25) days. Vasculitis occurred after the first vaccine dose in most patients (n = 8). All patients had skin involvement, with skin necrosis in 4 patients. In total, 7 patients had joint involvement and 2 had arthritis. A total of 4 patients had nonsevere gastrointestinal involvement and 2 had nonsevere renal involvement. The median C-reactive protein level was 26 (IQR 10-66.75) mg/L, the median creatininemia level was 72 (IQR 65-81) µmol/L, and 1 patient had an estimated glomerular filtration rate of less than 60 mL/min at management. All patients received treatment, including 9 patients (75%) who received glucocorticoids. In total, 5 patients received a vaccine dose after developing IgAV, 1 of whom experienced a minor cutaneous relapse.

Conclusion. The baseline presentation of IgAV following COVID-19 vaccination was mild to moderate, and outcomes were favorable. Thus, a complete COVID-19 vaccination regimen should be completed in this population. Of note, a fortuitous link cannot be ruled out, requiring a worldwide pharmacovigilance search to confirm these findings.

Key Indexing Terms: COVID-19 vaccine, Henoch-Schönlein purpura, IgA vasculitis

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IgA vasculitis (IgAV) is an immune complex vasculitis[1] that mainly affects the small vessels.[2] Initial disease presentation is more severe in adults, with short-term prognosis affected mainly by gastrointestinal involvement, while kidney damage affects long-term morbidity and mortality.[3-5] IgAV usually occurs after an infection of the respiratory or digestive mucosa but can also be induced by a vaccine. The most frequently reported vaccines associated with IgAV are the influenza vaccine and the diphtheria, tetanus, and pertussis vaccine.[6-8]

After the coronavirus disease 2019 (COVID-19) pandemic outbreak, a worldwide vaccination campaign was undertaken,[9] using mainly a new mRNA-based technology.[10] Several autoimmune manifestations following COVID-19 vaccination have been reported, such as thrombotic thrombocytopenia, Guillain Barré syndrome, and myocarditis.[11,12] A few cases of vasculitis have also been reported, most being antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, or IgAV.[12-15]

Here, we aimed to report the first case series of IgAV associated with COVID-19 vaccination to study the patients' baseline presentations and outcomes.

METHODS

This national, multicenter, retrospective study included observations of

adult IgAV following COVID-19 vaccination between January 1, 2020, and January 1, 2022, in France. Participating centers were contacted through the network of the French National Society of Internal Medicine, the rare disease network (ie, la filière de santé des maladies auto-immunes et auto-inflammatoires rares), and the French Vasculitis Study Group.

Patients. IgAV was defined as follows: (1) presence of purpura with at least 1 other organ involved, including the kidneys, joints, or intestinal tract, and histologically proven small-vessel vasculitis (ie, leukocytoclastic vasculitis) with or without IgA deposits or (2) isolated purpura and histologically proven small-vessel vasculitis (ie, leukocytoclastic vasculitis) with deposits of IgA. All patients were screened negative for both ANCA and cryoglobulinemia. Patients with new-onset IgAV occurring after a COVID-19 vaccination were included. The maximum time between vaccination and onset of vasculitis symptoms was set at 4 weeks to maintain reasonable accountability.[16]

Ethical considerations. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Procedures for data collection and management of included patients were approved by the Commission Nationale Informatique et Libertés under registration number F20220203141812 (MR-004). Per the Jardé law in France regarding research involving human participants, patients gave their nonopposition to be included in the study and to the processing of their data.

Data collection. All clinicians used a standardized form to collect the demographic data—age, sex, and comorbidities—of each included patient. Regarding vaccination, the vaccine name, number of injections, time to IgAV onset, and relapse after new vaccination were recorded. Regarding IgAV, general symptoms, baseline organ involvement, and disease characteristics were recorded. Skin and kidney biopsy findings using the classification by Pillebout et al[5] for renal involvement were also recorded. Laboratory parameters, including C-reactive protein (CRP), creatininemia, estimated glomerular filtration rate (eGFR) assessed with the Modification of Diet in Renal Disease (MDRD) equation,[17] proteinuria, and IgA count, were collected when available. Proteinuria was defined as 24-hour urine protein excretion of greater than 0.5 g/day. Hematuria was defined as the presence of greater than 10 red blood cells/mm^3 in the urine; hematuria was considered macroscopic if more than 1500 red blood cells/mm^3 were present in the urine. Elevated IgA levels were defined as IgA greater than 3.5 g/L. Treatments used for IgAV onset and relapse were compiled.

Statistical analysis. Descriptive statistics included median (IQR) for continuous variables and frequency (percentage) for categorical variables using Prism (version 9.2.0; GraphPad).

RESULTS

In total, 12 patients were included from 12 centers; 5 of these were women (41.7%). The median age was 52.5 (IQR 30.75-60.5) years.

Vaccination. Most patients received an mRNA vaccine: 7 patients (58%) were vaccinated with the BNT162b2 vaccine and 3 (25%) were vaccinated with the mRNA1273 vaccine. In total, 2 patients received a viral vector vaccine (ChAdOx1). In 8 patients (66.7%), vasculitis occurred after the first vaccine dose: 5 cases (62.5%) after BNT162b2 vaccination, 2 cases (25%) after mRNA1273 vaccination, and 1 case (12.5%) after ChAdOx1 vaccination. In total, 3 patients (25%) developed IgAV after the second vaccine dose: after BNT162b2 vaccination in 2 cases (66.7%) and after a second dose of ChAdOx1 in 1 case (33.3%). Only 1 patient (8%) was diagnosed after the third vaccine dose. Vaccination characteristics are given in Table 1.

The median time from vaccination to onset of symptoms was 11.5 (IQR 4.25-21.25) days for all vaccines and all vaccination schedules combined. The median times from vaccination to IgAV onset categorized by number of doses and vaccine received are summarized in Figure 1. The median time to disease onset regarding the number of doses is as follows: first dose, 18 (IQR 8.3-24.3) days; second dose, 5 (IQR 4-14) days; and third dose, 1 day. The median time to disease onset regarding the vaccine used is as follows: BNT162b2, 14 (IQR 8-25) days; mRNA1273, 17 (IQR 1-22) days; and ChAdOx1, 4.5 (range 4-5) days.

IgAV baseline characteristics. In total, 3 patients (25%) presented with constitutional symptoms (ie, asthenia) during the onset of IgAV. Purpura involved lower limbs in 11 cases (92%; 1 missing data point), upper limbs in 9 cases (75%; 1 missing data point), and the abdomen in 4 cases (33%). Necrotic lesions were observed in 4 cases (33%), and hemorrhagic bullae were identified in 2 cases (17%).

In total, 7 patients had joint involvement (58%): 4 cases (57%) involved the upper and lower limbs and 2 cases (29%) involved the lower limbs alone (1 missing data point). Of note, arthritis was present in 2 patients (29%), affecting the joints of the upper and lower limbs in all cases.

In total, 4 patients had digestive involvement (33%), all with abdominal pain; these were associated with diarrhea in 2 cases. In all cases, an abdominal scan was performed; a thickened wall was found in 2 cases. An upper esophagogastroduodenoscopy was performed in 1 case and found petechial purpura lesions associated with erosive lesions. In total, 2 patients had renal involvement (17%), 1 of whom had edema of the lower limbs.

The median CRP was 26 (IQR 10-66.75) mg/L, the median creatinine was 72 (IQR 65-81) μmol/L, and the median eGFR calculated by MDRD was 102 (IQR 86.5-120) mL/min/1.73 m^2. The median albumin level was 40 (IQR 32.25-43.75) g/L (normal range is 30-45 g/L).

A skin biopsy was performed in 12 cases (100%). All had leukocytoclastic vasculitis lesions associated with fibrinoid necrosis in 2 cases (17%). IgA deposits in small vessels were found in 9 cases (75%). One renal biopsy was performed, which revealed a mesangiopathic IgA glomerulonephritis without any endo- or extracapillary proliferation (ie, class I of the Pillebout classification). Clinical and biological parameters are summarized in Table 2.

Treatment. All patients received treatment. Of these, 8 patients received oral glucocorticoids (GCs; 66%), after a pulse of methylprednisolone for 1 patient. One was treated with 2 pulses of 500 mg methylprednisolone without relay with oral GCs. In total, 4 patients were treated with colchicine (33%): 3 (75%) as monotherapy and 1 (25%) in combination with GC. Data are summarized in Table 2.

General outcome and outcome after a new COVID-19 vaccine dose. The median follow-up time was 6 (IQR 5.25-8.25) months. Out of 12 patients, 1 (8%) presented with a relapse of his disease without any additional vaccination at 3 months. He presented with a renal relapse without the need for a kidney biopsy and was not treated at that time (Table 2).

In total, 5 patients received at least 1 booster of the COVID-19 vaccine (3 missing data points) after onset of symptoms, all with the mRNA vaccine. Out of those patients, 4 were

Table 1. Vaccine characteristics for each patient.

Patient No.	Sex	Age, yrs	Vaccine Doses Before Onset of Vasculitis, n	Vaccine	Time Before Symptoms, days	Relapse After New Vaccination
1	Female	82	2	ChAdOx1	5	Missing data
2	Male	20	1	mRNA1273	22	Missing data
3	Male	16	1	BNT162b2	25	Missing data
4	Male	62	2	BNT162b2	14	No new vaccination
5	Male	56	1	ChAdOx1	4	No relapse after 2 other doses of BNT162b2
6	Male	66	1	mRNA1273	17	No relapse after a second dose of mRNA1273
7	Female	52	3	mRNA1273	1	No new vaccination
8	Male	29	2	BNT162b2	4	No new vaccination
9	Female	51	1	BNT162b2	19	No relapse after 2 other doses of BNT162b2
10	Female	36	1	BNT162b2	9	Minimal skin relapse after the second injection (mRNA1273)
11	Female	56	1	BNT162b2	28	No relapse after the third dose of BNT162b2
12	Male	53	1	BNT162b2	8	No new vaccination

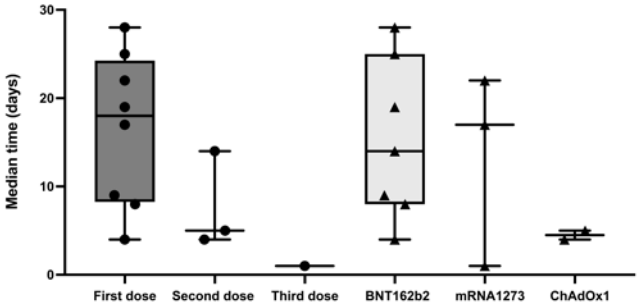

Figure. Median time before IgAV onset categorized by number of doses and vaccine received. Median time is given in days with the corresponding IQR. IgAV: IgA vasculitis.

treated at that time: 2 with GCs and 2 with colchicine. Out of the 5 patients, 1 had a cutaneous relapse of IgAV and was treated with colchicine at that time (Tables 1 and 2).

DISCUSSION

In this paper, we report the first case series including 12 patients who presented with IgAV following vaccination against COVID-19, providing similar data on both presentation and outcome regarding IgAV of other etiologies.[18]

So far, reports of IgAV following vaccination against COVID-19 have been scarce.[19] Of the 11 cases reported in adults, 9 were new-onset vasculitis following vaccination and 2 were relapses of 1 previously proven and 1 presumed IgAV. Compared to our case series, the median age of all patients as determined from the literature analysis was higher—62 (IQR 33-76) years vs 52.5 (IQR 30.75-60.5) years—and the male to female ratio was lower: 1 vs 1.4, respectively. Baseline digestive and renal involvement were rare in our cohort, representing 33% and 17% of the cases. Of note, no life-threatening organ involvement was observed in either our study or in the literature, with the exception of 1 patient in the literature who presented with renal involvement during the course of IgAV and required cyclophosphamide.[19]

Interestingly, despite the low percentage of patients with digestive or renal involvement in our series, the proportion of patients treated with oral or intravenous GCs was 75% and 50%, respectively, in the literature. This finding illustrates the absence of harmonized worldwide guidelines for the treatment of adult patients with IgAV,[19] despite comparable IgAV severity profiles.

In all patients, the most frequently administered vaccine was an mRNA vaccine (BNT162b2). This is probably because it is one of the most widely available vaccines, especially in France where it was used in 78.1% of cases for the first injection.[20] Also, in agreement with the literature, most cases of IgAV were triggered following the first dose of vaccine in our cohort (66.6%), which is in agreement with the literature (53%). Nonetheless, relapses of de novo IgAV following COVID-19 vaccination after a new vaccine dose (eg, the second or the third dose) may also occur. In our study, 1 patient relapsed out of 5 patients who received at least 1 booster after the onset of symptoms (3 missing data points), as seen in the literature. The relapse was benign in our patient, with cutaneous manifestations, unlike the one seen in the literature who developed renal involvement without any proliferative lesions.[21]

Several hypotheses have been put forward to explain the occurrence of autoimmune disease following COVID-19 vaccination. Interestingly, regarding the occurrence of IgAV, it has been shown that in addition to IgG production after COVID-19 vaccination, IgA production occurs following the BNT162b2 and ChAdOx1 vaccines.[22,23] To be more precise, an IgA serum peak is observed 11 days after the first vaccine injection and 7 days following the second injection. As SARS-CoV-2 enters its host through the pulmonary tract, it is essential to have an enhanced first-line IgA defense at this site to achieve better vaccine efficacy. Hypoglycosylated IgA plays a pivotal role during the onset of IgAV. It forms immune complexes, which further activate the immune system.[24] Hence, we hypothesize that vaccination in these patients induced an IgA-mediated response, probably in hosts with a Ig-glycosylation enzyme deficiency.

Obviously in the present study, we cannot rule out an incidental link between IgAV and vaccines, given the total number

Table 2. Characteristics, treatment, and outcomes of IgA vasculitis.

Patient No.	Skin and Joint Involvement	Gastrointestinal Involvement	Kidney Involvement	Biological Parameters	Treatment	Outcome
1	· Vascular purpura of the upper and lower limbs · Knee and ankle arthralgia	· Abdominal pain and diarrhea · No abnormalities on abdominal CT	· Lower limb oedema · Microscopic hematuria without proteinuria and kidney failure with creatininemia at 250 µmol/L	· CRP: 75 mg/L · Albumin: 34.4 g/L · Creatininemia: 250 µmol/L · eGFR (MDRD): 16 mL/min/1.73 m^2 · IgA count: not available	Two intravenous pulses of methylprednisolone	No relapse at 6 months of follow-up
2	· Vascular purpura of the upper and lower limbs and abdomen · Elbow and ankle arthralgia	–	–	· CRP: 8.1 mg/L · Albumin: 45.1 g/L · Creatininemia: 82 µmol/L · eGFR (MDRD): 120 mL/min/1.73 m^2 · IgA count: not available	GCs at 20 mg/day	No relapse at 1 year of follow-up
3	· Vascular purpura of the upper and lower limbs with necrotic lesions · Left wrist and ankle arthritis	–	· Lower limb oedema · Microscopic hematuria without proteinuria	· CRP: 38.9 mg/L · Albumin: 39.2 g/L · Creatininemia: 61 µmol/L · eGFR (MDRD):142 mL/min/1.73 m^2 · IgA count: 7.5 g/L	GCs at 35 mg/day	No relapse at 1 year of follow-up
4	· Vascular purpura of the upper and lower limbs and abdomen with necrotic lesions	–	· Microscopic hematuria without proteinuria	· CRP: 2.3 mg/L · Albumin: 40 mg/L · Creatininemia: 70 µmol/L · eGFR (MDRD): 98 mL/min/1.73 m^2 · IgA count: not available	Colchicine	No relapse at 6 months of follow-up
5	· Vascular purpura of the upper and lower limbs and abdomen	· Abdominal pain · No abnormalities on abdominal CT	–	· CRP: 10 mg/L · Albumin: 46 g/L · Creatininemia: 73 µmol/L · eGFR (MDRD): 88 mL/min/1.73 m^2 · IgA count: 7.42 g/L	GCs at 60 mg/day	No relapse at 6 months of follow-up
6	· Vascular purpura of the upper and lower limbs	· Abdominal pain and diarrhea · Thickening of the walls of the digestive tract on abdominal CT	–	· CRP: 38 g/L · Albumin: 30 g/L · Creatininemia: 65 µmol/L · eGFR (MDRD): 106 mL/min/1.73 m^2 · IgA count: not available	GCs at 60 mg/day	Kidney relapse at 3 months, with no histology; no disease activity at 6 months
7	· Vascular purpura of the upper and lower limbs and abdomen with necrotic lesions and hemorrhagic bullae · Widespread arthralgia	–	–	· CRP: 10 mg/L · Albumin: 43 g/L · Creatininemia: 50 µmol/L · eGFR (MDRD): 112 mL/min/1.73 m^2 · IgA count: not available	GCs at 30 mg/day	Increase of GCs to 60 mg/day at 1 week because of no control of symptoms; disease duration of 1 month at inclusion

Table 2. Continued.

Patient No.	Skin and Joint Involvement	Gastrointestinal Involvement	Kidney Involvement	Biological Parameters	Treatment	Outcome
8	· Vascular purpura of the upper and lower limbs with necrotic lesions and hemorrhagic bullae · Ankle arthralgia	–	–	· CRP: 10 mg/L · Albumin: 39.4 g/L · Creatininemia: 72 µmol/L · eGFR (MDRD): 120 mL/min/1.73 m^2 · IgA count: 3.45 g/L	GCs at 40 mg/day and colchicine	Disease duration of 1 month
9	· Vascular purpura of the upper and lower limbs · Widespread arthralgia	–	· Microscopic hematuria without proteinuria	· CRP: 42 mg/L · Albumin: 42.7 g/L · Creatininemia: 72 µmol/L · eGFR (MDRD): 84.5 mL/min/1.73 m^2 · IgA count: 4.48 g/L	Colchicine	Arthralgia at 5 months
10	· Vascular purpura of the upper and lower limbs	–	–	· CRP: 14 g/L · Albumin: 33 g/L · Creatininemia: 78 µmol/L · eGFR (MDRD): 77 mL/min/1.73 m^2 · IgA count: 2.05 g/L	Colchicine	Skin relapse after the second vaccination at 5 months; no disease activity at 6 months
11	· Vascular purpura of the lower limbs	–	–	· CRP: 13.2 mg/L · Albumin: 40 mg/L · Creatininemia: 65 µmol/L · eGFR (MDRD): 91 mL/min/1.73 m^2 · IgA count: not available	GCs at 100 mg/day	No relapse at 6 months of follow-up
12	· Vascular purpura of the abdomen and the lower limbs · Hand, knee, and ankle arthritis	· Abdominal pain with thickening of the walls of the digestive tract on abdominal CT · Petechial purpura and parietal erosion by OGD fibroscopy	· Microscopic hematuria and proteinuria at 1.7 g/L	· CRP: 209 mg/L · Albumin: 43.4 g/L · Creatininemia: 92 µmol/L · eGFR (MDRD): 82 mL/min/1.73 m^2 · IgA count: not available	Intravenous pulse of 500 mg of methylprednisolone (×3), followed by GCs at 80 mg/day	New intravenous pulse of 180 mf of methylprednisolone at day 6 for uncontrolled abdominal pain under GCs; no relapse at 9 months of follow-up

CRP: C-reactive protein; CT: computed tomography; eGFR: estimated glomerular filtration rate; GC: glucocorticoid; MDRD: Modification of Diet in Renal Disease; OGD: oesophagogastroduodenoscopy.

of vaccines administered worldwide and the lack of difference in terms of baseline presentation with the adult IgAV not induced by COVID vaccination that was reported in the IGAVAS study.[18] However, we can emphasize some facts extolling a causal link. First, we can state that IgAV is a rare disease, especially in adults, with an incidence rate estimated at 1 per 1 million person-years.[25] Further, its incidence may have decreased since the beginning of the COVID-19 pandemic. Indeed, both the lockdown measures applied in many countries and systematic mask-wearing could have led to a decrease in the incidence of IgAV induced by other pathogens.[9] Then, we highlight the very short time between vaccination and the onset of symptoms (11 days). Lastly, a relapse occurring after a subsequent vaccine dose is also a strong argument for a causal link between the 2 conditions, vaccination already being a suspected risk factor for IgAV.[16]

In our cohort, 80% of patients were treated when administered a new booster, which may explain the nonsystematic relapse of IgAV. This raises the question of whether vaccinations should be monitored in patients receiving treatment with GCs or colchicine, as relapse is a fear for many of these patients.

In conclusion, this first case series describes 12 patients presenting with IgAV following COVID-19 vaccination. The baseline presentation was mild to moderate, and outcomes were mostly favorable, even though minor cutaneous relapse could occur after a further vaccine dose. Thus, a complete COVID-19 vaccination regimen should be completed in this population. However, a fortuitous link cannot be ruled out, requiring a pharmacovigilance approach to assess a potential safety signal with COVID-19 vaccines in the field of IgAV.

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