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Immunoglobulin A Vasculitis Following COVID-19: A French Multicenter Case Series

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ABSTRACT. ***Objective.*** Immunoglobulin A vasculitis (IgAV) usually occurs following viral respiratory tract infection. In the context of the global coronavirus disease 2019 (COVID-19) pandemic, we describe a case series of patients who developed IgAV following SARS-CoV-2 infection.

Methods. This national multicenter retrospective study included patients with IgAV following SARS-CoV-2 infection from January 1, 2020, to January 1, 2022. Patients had histologically proven IgAV and reverse transcription PCR (RT-PCR)-proven SARS-CoV-2 infection. The interval between infection and vasculitis onset had to be < 4 weeks.

Results. We included 5 patients, 4 of whom were women with a mean age of 45 years. Four patients had paucisymptomatic infections and 1 required a 48-hour low-flow oxygen treatment. All 5 patients had purpuric skin involvement. Arthritis was observed in 2 patients, 3 had IgA glomerulonephritis, and 2 had digestive involvement. Three renal biopsies were performed and showed mesangial IgA deposits without any extracapillary proliferation. Median C-reactive protein was 180 (range 15.1-225) mg/L, median serum creatinine level was 65 (range 41-169) µmol/L, and 2 patients had a glomerular filtration rate < 60 mL/min. Four patients received first-line treatment with glucocorticoids. All patients had a favorable progression and 2 patients experienced minor skin relapses, one after COVID-19 vaccination.

Conclusion. This series describes the emergence of IgAV closely following COVID-19; we were not able to eliminate an incidental link between these events. Their disease outcomes were favorable. In most of our patients, the SARS-CoV-2 infection was paucisymptomatic, and we recommend RT-PCR tests to look for COVID-19 in patients without any evident triggers for IgAV.

Key Indexing Terms: COVID-19, Henoch-Schonlein purpura, IgA vasculitis, SARS-CoV-2

Immunoglobulin A (IgA) vasculitis (IgAV) is an immune complex vasculitis[1] that mainly affects small vessels in the skin, gastrointestinal (GI) tract, kidney, and joints.[2] It tends to affect children[3]; in adults, classically, the disease has a more severe initial presentation.[4] It usually occurs following bacterial or viral infections. The short-term prognosis is influenced by gastrointestinal (GI) involvement, whereas long-term morbimortality is affected by kidney damage.[5]

The SARS-CoV-2 virus infection causing the respiratory disease coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020.[6] Like many respiratory diseases, in temperate countries such as France it has been shown to have seasonality.[7] COVID-19 could be responsible for the onset or relapse of several autoimmune diseases.[8-10]

The link between respiratory infections and IgAV is well known, and the pandemic further brought this out in research in terms of cases of IgAV following COVID-19. Herein, we report a short case series, describing clinical presentation, management, and outcomes of such cases.

METHODS

Settings. This national multicenter retrospective study included patients with IgAV that followed SARS-CoV-2 infection between January 1, 2020, and January 1, 2022.

Patients. All patients with histologically proven IgAV and a SARS-CoV-2 infection proven by reverse transcription PCR (RT-PCR) were enrolled. The maximum delay between infection and onset of vasculitis symptoms was set at < 4 weeks.

Ethics. This study was performed in accordance with the ethical standards of the Declaration of Helsinki. Procedures for data collection and

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The authors declare no conflicts of interest relevant to this article.

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the management of included patients were approved by the Commission Nationale de L'Informatique et des Libertés under the registration number F20220203141812 (MR-004).

Data collection. All clinicians had to complete a case report form for every patient, which included demographics data (age, sex), comorbidities, IgAV and a description of the SARS-CoV-2 infection (need of oxygen therapy or intensive care, prior COVID-19 vaccination, date of diagnosis), as well as biological and pathological data.

Statistical analysis. Descriptive statistics included medians with IQRs for continuous variables and frequencies (percentages) for categorical variables using Microsoft Excel (version 16.59).

RESULTS

Patient 1. A 57-year-old male patient, with a medical history of alcoholic and metabolic cirrhosis and without any history of purpura or glomerulonephritis, was diagnosed with IgAV. The patient had a paucisymptomatic SARS-CoV-2 infection with cough, fever, and asthenia, while awaiting a third dose of the COVID-19 vaccine (previous vaccintion was 6 months prior). The time between COVID-19 onset and the first IgAV symptoms was 7 days.

The first manifestations of IgAV were vascular purpura of the upper and lower limbs and abdomen and arthritis of the ankles and knees, rapidly followed by abdominal pain and edema of the lower limbs. The C-reactive protein (CRP) at initial management was 15.1 mg/L, with creatinine at 67 μmol/L, albumin at 25 g/L, microscopic hematuria and proteinuria evaluated at 2.7 g/24 h, and an elevated IgA level of 7.19 g/L. Abdominal computed tomography (CT) showed signs of ileitis. Histological analysis of skin biopsy showed IgA deposits in cutaneous vessels.

To manage the GI involvement of IgAV, intravenous (IV) pulses of 125 mg of methylprednisolone (MP) were administered for 3 consecutive days relayed by glucocorticoids (GCs), namely prednisone, at 1 mg/kg/day with 2-month tapering. Initial response was favorable but 2 weeks after discharge, while still on prednisone, the edema of the lower limbs became aggravated with new skin lesions. Nephrotic syndrome was diagnosed and a kidney biopsy was performed, showing mesangial IgA deposits with endocapillary proliferation only. A maintenance regimen of 1 mg/kg/day of prednisone for 1 month was decided, followed by a 6-month tapering associated with an angiotensin II receptor antagonist (ARAII). At 4 months, the patient presented with increased proteinuria as a result of discontinuation of ARAII, with proteinuria at 6 g/24 h and creatinine at 108 μmol/L. The tapering of prednisone was stopped for 1 month and ARAII was reintroduced, resulting in a decrease of proteinuria at 1 month, and normalization of creatinine and discontinuation of prednisone at 2 months, without further relapse.

Patient 2. A 41-year-old female patient with no prior comorbidities was referred for polyarthritis. The patient had a paucisymptomatic SARS-CoV-2 infection with cough, fever, asthenia, anosmia, and dyspnea without needing oxygen therapy; no COVID-19 vaccine was available at the time. The time between COVID-19 onset and the first symptoms of IgAV was 15 days.

The first manifestations were vascular purpura of the lower limbs and arthritis of the elbows, ankles, and right knee. Kidney involvement with nephrotic syndrome and ear-nose-throat (ENT) involvement with nosebleeds were observed.

The CRP at initial management was 225 mg/L, with creatinine of 41 μmol/L, albumin of 19 g/L, microscopic hematuria and proteinuria at 3.7 g/24 h, and IgA level of 1.71 g/L. Abdominal CT was normal. The kidney biopsy showed glomerulonephritis with endocapillary proliferation with mild extracapillary proliferation and mesangial IgA deposits.

To manage renal involvement, IV pulses of 20 mg of MP for 5 consecutive days relayed by GCs, namely prednisone, at 1 mg/kg were given, with progressive tapering for 6 months. Follow-up at 7 months showed no sign of skin, ENT, or kidney relapse, and a complete resolution of proteinuria.

Patient 3. A 61-year-old female patient with a 7-year prior diagnosis of antineutrophil cytoplasmic antibody (ANCA)-negative necrotizing vasculitis, with neurological and skin involvement and without IgA deposit, was referred for SARS-CoV-2 infection and relapsing vasculitis. The patient presented with a paucisymptomatic SARS-CoV-2 infection with fever and diarrhea, and was not vaccinated. The time between COVID-19 onset and the first symptoms of IgAV was 15 days. The first manifestation was vascular purpura of the upper and lower limbs. The baseline CRP was 135 mg/L, with creatinine of 169 μmol/L, albumin of 28 g/L, and microscopic hematuria and proteinuria measured at 0.7 g/24 h; IgA count was not available.

The histological analysis of skin biopsy found leukocytoclastic vasculitis without IgA deposit. To confirm the renal involvement, a kidney biopsy was performed, finding IgA deposits in glomeruli mesangium without any extracapillary proliferation.

A first-line treatment of prednisone at 1 mg/kg/day was started and was complicated after 3 days by *Campylobacter jejuni* and *Klebsiella oxytoca* colitis and a sacral eschar. GCs were suspended after 21 days because of uncontrolled cutaneous complications of the sacral eschar. At 3 months after GCs suspension, a cutaneous relapse occurred, and prednisone was reintroduced at 1 mg/kg/day. Three weeks after resuming GCs, there were behavioral and phasic disorders with insomnia; GCs were quickly tapered for 1 month and mycophenolate mofetil (MMF) was introduced. Finally, 3 weeks after, the patient was switched to azathioprine (AZA) and colchicine due to new psychiatric and skin manifestations. The patient was then lost to follow-up.

Patient 4. A 24-year-old female patient with no prior comorbidities was referred for vascular purpura. She had a paucisymptomatic SARS-CoV-2 infection with cough, fever, and asthenia; no COVID-19 vaccine was available at the time. The time between COVID-19 onset and the first symptoms of IgAV was 27 days. The first manifestations were vascular purpura of the upper and lower limbs and arthralgia in the ankles. The baseline CRP was not available, and creatinine was at 65 μmol/L with no proteinuria or microscopic hematuria. IgA count was not available. Histological analysis of skin biopsy showed leukocytoclastic vasculitis and IgA deposits in cutaneous vessels. No treatment was initiated. Progression was stable with few skin relapses during the first year of follow-up and after the first vaccination against SARS-CoV-2 with the

Bnt162b2 mRNA SARS-CoV-2 vaccine, without need of specific treatment.

Patient 5. A 52-year-old female patient, with no prior comorbidities was referred for SARS-CoV-2 infection with vascular purpura and abdominal pain. She presented with a SARS-CoV-2 infection requiring low-flow oxygen therapy; no COVID-19 vaccine was available at that time. The time between COVID-19 onset and the first symptoms of IgAV was 13 days. First manifestations were vascular purpura of the upper and lower limbs and abdominal pain. The baseline CRP was 60 mg/L, with creatininemia of 43 µmol/L without proteinuria or microscopic hematuria. IgA count was not available.

Histological analysis of skin biopsy found leukocytoclastic vasculitis and IgA deposits in cutaneous vessels. Abdominal CT showed a parietal thickness with submucosal edema and segmentary damages, and the esogastroduodenal endoscopy did not reveal any histological signs of vasculitis abnormalities.

Given the abdominal involvement, IV pulses of 250 mg of MP were administered for 3 consecutive days relayed by GCs at 1 mg/kg/day and gradually tapered. Follow-up after 9 months showed no sign of relapse.

All main demographic and clinical patient characteristics are summarized in Table 1.

DISCUSSION

Herein, we reported the first case series, to our knowledge, of 5 patients with IgAV closely following COVID-19. Nowadays, there are robust arguments linking IgAV to infections, particularly those of the respiratory tract.[11] The pathophysiological hypothesis is that a mucosal infection leads to an overproduction of interleukin 6 (IL-6) resulting in the synthesis of galactose-deficient IgA1. They form immune complexes and induce vasculitis damage.[12] SARS-CoV-2 may be responsible for the so-called cytokine storms, including increased IL-6 production.[13,14]

In view of respiratory tract involvement, the cytokine storm in some patients with COVID-19 taken together with the 22 million people infected with COVID-19 at some point in France,[15] we could have expected an increase in the number of IgAV cases during the pandemic. On the contrary, according to our data and the literature, IgAV seems to remain a very rare disease.

To our knowledge, 14 cases of IgAV following COVID-19 have been reported so far, excluding ours, and 6 of them were observed in children.[16-18] In our series, the median age was 45 years, similar to that reported in the adult cases from the literature. In the previously reported cases, the SARS-CoV-2 infection mostly was not severe and did not require oxygen therapy. Only 3 cases of severe infection were reported. All 3 required hydroxychloroquine and lopinavir/ritonavir, 2 were treated in association with tocilizumab, and 1 needed continuous positive airway pressure.[19-21] The baseline manifestations of vasculitis in our study agree with those reported in the literature.

Five adult patients (62.5%) were treated with GCs in the literature specifically for vasculitis symptoms, and one of them in combination with rituximab for a rapid deterioration of renal function, as compared to 4 (80%) treated with GCs in our cohort.[19] The data regarding progression seem rather reassuring in both our cohort and the literature, even though follow-up was short. Only 1 of our patients who had received the Bnt162b2 mRNA SARS-CoV-2 vaccine (data missing for 1 patient) experienced a moderate skin relapse after the first dose, which is not sufficient to form any conclusions or recommendations.

Understanding why there are so few IgAV cases following SARS-CoV-2 infection reported would require further epidemiological and experimental studies. The mandated wearing of masks as well as the containment measures taken in many countries could have led to a decrease in IgAV induced by other pathogens, but it does not explain the scarce case reports of IgAV following SARS-CoV-2 infection.

Of course, the total number of IgAV cases following SARS-CoV-2 infection around the world is not known. It was not possible to establish the true incidence of IgAV following SARS-CoV-2 infection in France over the studied period, and we also did not include pediatric forms. However, IgAV are histologically confirmed in all our observations, which was not necessarily the case in all observations reported in the literature. To maintain a reasonable presumption of imputability, we included all SARS-CoV-2 infections documented within a 4-week delay before the onset of IgAV. Additionally, all our cases, except maybe patient 2, are de novo IgAV regarding the absence in their medical history of vasculitis rash, arthritis, or renal involvement.

The progression of IgAV following SARS-CoV-2 infection remains reassuring. It is interesting to note that since 3 patients (21%) in the literature and 2 patients (40%) in our cohort presented a comorbidity such as cirrhosis, regular alcohol consumption or autoimmune disease. These underlying conditions may have favored the occurrence of IgAV.[19,22,23]

Despite the small number of cases reported here, the outcome of patients with IgAV following SARS-CoV-2 infection appears favorable. In most of our patients, the SARS-CoV-2 infection was paucisymptomatic, prompting an RT-PCR test to look for COVID-19 in patients without any evident triggers of IgAV.

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Table 1. Demographic and clinical characteristics of patients with IgAV following a SARS-CoV-2 infection.

Patient	Sex/Age, yrs	No. of COVID-19 Vaccinations Before Infection	Comorbidities	COVID-19 Symptoms	Initial Organ Involvement	Initial Biological Variables	Treatment	Progression	Relapse After COVID-19 Vaccination	Follow-up Duration at Inclusion, mos
1	M/57	2	Alcoholic and metabolic cirrhosis	Paucisymptomatic (cough, fever, asthenia)	Vascular purpura of the upper and lower limbs and abdomen, arthritis in the ankles and knees, abdominal pain and ileitis, kidney involvement (nonproliferative IgA nephropathy).	CRP: 15.1 mg/L Creatinine: 67 µmol/L Proteinuria: 2.7 g/24 h IgA: 7.19 g/L	IV MP (125 mg/d × 3) relayed by GC 1 mg/kg No specific COVID-19 treatment	At 4 mos after hospital discharge: aggravated proteinuria at 6 g/24 h, with creatinine at 108 µmol/L. No abdominal pain, no skin involvement.	No new vaccination	6
2	F/41	0	No comorbidities	Paucisymptomatic (cough, fever, asthenia)	Vascular purpura of the lower limbs. Arthritis in the elbows, ankles, and right knee. Kidney involvement with nephrotic syndrome (nonproliferative IgA nephropathy). Nosebleeds with ENT involvement.	CRP: 225 mg/L Creatinine: 41 µmol/L Proteinuria: 3.7 g/24 h IgA: 1.71 g/L	IV MP (20 mg/d × 5) relayed by GC 1 mg/kg No specific COVID-19 treatment	No relapse.	No relapse	7
3	F/61	0	7-yr prior diagnosis of necrotizing vasculitis, with ANCA negativity treated by CYC and AZA	Paucisymptomatic (fever, diarrhea)	Vascular purpura of the upper and lower limbs. Kidney involvement (nonproliferative IgA nephropathy).	CRP: 135 mg/L Creatinine: 169 µmol/L Proteinuria: 0.7 g/24 h IgA: none	GC 1 mg/kg	Prednisone discontinuation at 3 wks because of uncontrolled cutaneous complications of the sacral eschar. Cutaneous relapse at 3 mos without treatment: reintroduction of prednisone 1 mg/kg/d with psychiatric side effects at 3 wks. Introduction of MMF. Skin relapse at 3 wks after MMF introduction with new psychiatric manifestation. Switch to AZA and colchicine.	No vaccination	4
4	F/24	0	No comorbidities	Paucisymptomatic (cough, fever, asthenia)	Vascular purpura of the upper and lower limbs. Ankle arthralgia.	CRP: none Creatinine: 65 µmol/L Proteinuria: negative IgA: none	No treatment	Persistent skin relapses after 6 and 12 mos.	Skin relapse after the first injection of Bnt 162b2 mRNA vaccine. No relapse of the disease after the second vaccination.	13
5	F/52	0	No comorbidities	Dyspnea with O_2 therapy, 1 L/min for 48 h	Vascular purpura of the upper and lower limbs. Abdominal pain with parietal thickness and edema without ileitis.	CRP: 60 mg/L Creatinine: 43 µmol/L Proteinuria: negative IgA: none	IV MP (250 mg/d × 3) relayed by GC 1 mg/kg No specific COVID-19 treatment	No relapse.	No information	9

ANCA: antineutrophil cytoplasmic antibody; AZA: azathioprine; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CYC: cyclophosphamide; ENT: ear-nose-throat; GC: glucocorticoid; IgA: immunoglobulin A; IgAV: IgA vasculitis; IV: intravenous; MMF: mycophenolate mofetil; MP: methylprednisolone.

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