IgA vasculitis following COVID-19: a French multicentric case-series

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Abstract:

**Introduction:** IgA vasculitis (IgAV) usually occurs following viral respiratory tract infection. The SARS-CoV-2 infection has spread over the world. In this context, we describe a case series of patients who developed IgAV following SARS-CoV-2 infection.

**Patients and methods:** This national multicentre retrospective study included patients with IgAV following SARS-CoV-2 infection, from the 1 January 2020 and 1 January 2022. Patients had histologically proven IgAV and RT-PCR proven SARS-CoV-2 infection. The interval time between infection and vasculitis onset had to be less than 4 weeks.

**Results:** We included 5 patients, 4 of them women with a mean age of 45 years. Four patients had paucisymptomatic infections and one required a 48-hours low-flow oxygen treatment. Five had purpuric skin involvement. Arthritis was observed in 2 patients, 3 had IgA glomerulonephritis and 2 had digestive involvements. Three renal biopsies were performed and showed mesangial IgA deposits without any extra-capillary proliferation. Median C-reactive protein was 180 mg/l [15.1-225], median serum creatinine level was 65 µmol/l [41-169], one patient had a glomerular filtration rate < 60 ml/min. Four patients received a first-line treatment, all with glucocorticoids. All patients had a favourable progression and 2 patients experienced minor skin relapses, one closely after COVID vaccination.

**Conclusion:** This series describes the emergence of IgAV closely following COVID-19 without us being able to eliminate an incidental link. Their outcome seems favourable. In most of our patients, the SARS-CoV-2 infection was pauci-symptomatic, encouraging an RT-PCR test to look for COVID-19 infection in patient without any evident trigger for IgAV.
Key messages:

- IgA vasculitis can occur after a SARS-CoV-2 infections, mostly after a pauci-symptomatic one
- IgA vasculitis following COVID-19 present favorable outcome
- RT-PCR test for COVID 19 is recommended when confronted with IgA vasculitis without a trigger

Keywords: IgA vasculitis, Henoch-Schonlein purpura, SARS-CoV-2, COVID-19
1. Introduction

IgA vasculitis (IgAV) is an immune complex vasculitis (1) that mainly affects small vessels in the skin, gastrointestinal tract, kidney, and joints (2). It tends to affect children (3) with classically, in adults, a more severe initial disease presentation (4). It usually occurs following bacterial or viral infections. The short-term prognosis is influenced by gastrointestinal involvement, while long term morbi-mortality is affected by kidney damages (5).

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

The link between respiratory infection and IgAV is well known, and the pandemic context brought out this research for cases of IgAV following COVID-19. Herein, we report a short case series, describing clinical presentation, management, and outcome of such cases.

2. Material and methods

2.1. Settings

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

2.2. Patients.

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

The study was performed in accordance with the ethical standards of the Helsinki declaration. Procedures for data collection and management of patients included were approved by the CNIL under the registration number F20220203141812 (MR-004).

2.3. Data collection
All clinicians had to complete a case report form for every patient, including demographics data (age, sex), comorbidities, IgAV and SARS-CoV-2 infection description as well as biological and pathological data.

2.4. Statistical Analysis

Descriptive statistics included the median, with interquartile range (IQR) for continuous variables, and frequency (percentage) for categorical variables using Microsoft® Excel, version 16.59.

3. Observations

Patient 1

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

First manifestations of IgAV were vascular purpura of the upper and lower limbs and abdomen, ankles and knees arthritis rapidly followed by abdominal pain and oedema of the lower limbs. The CRP at initial management was 15mg/l, with a creatininemia at 67 µmol/l, an albuminemia at 25g/l, a microscopic haematuria, proteinuria evaluated at 2.7 g/24h, and an elevated immunoglobulin A (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 gastrointestinal involvement of IgAV, it was decided to administer intravenous pulses of 125 mg of methylprednisolone for 3 consecutive days relayed by glucocorticoids, prednisone, 1mg/kg/day with 2 months tapering. Initial response was favourable but at two weeks after discharge, on prednisone, the oedema of the lower limbs became aggravated with new skin lesions. A nephrotic syndrome was diagnosed, and a kidney biopsy was performed, showing mesangial IgA deposits with endocapillary proliferation only. A maintenance regimen with 1 mg/kg/day of prednisone was decided for one month, followed by a 6 months tapering associated with an angiotensin II receptor antagonist (ARAII). At 4 months the patient presented with an increased proteinuria, due to adiscontinuation of ARAII with a proteinuria.
at 6g/24h and a creatininaemia at 108 µmol/l. The tapering of prednisone was stopped for one month and ARAII reintroduced with a negativation of proteinuria at 1 month, normalization of creatininemia and discontinuation of prednisone 2 months later without new relapse.

**Patient 2**

A 41-year-old female patient, with no prior comorbidities was referred for polyarthritis. She had a paucisymptomatic SARS-CoV-2 infection with cough, fever, asthenia, anosmia, and dyspnea without needing O2 therapy while no vaccine was available at the time. The time between the COVID-19 infection and the first symptoms of IgAV was 15 days. The first manifestations were vascular purpura of the lower limbs, and arthritis of elbows, ankles, and right knee. Kidney involvement with nephrotic syndrome, and ear nose and throat (ENT) involvement with nosebleed were observed.

The CRP at initial management was 225 mg/l, with a creatininemia of 41 µmol/l, albuminemia of 19g/l, a microscopic haematuria and proteinuria at 3.7 g/24h, IgA level was 1.71g/l. Abdominal-CT was normal. The kidney biopsy showed glomerulonephritis with endocapillary proliferation with mild extra capillary proliferation and mesangial IgA deposits.

To manage renal involvement, intravenous pulses of 20 mg of methylprednisolone for 5 consecutive days relayed by glucocorticoids, prednisone 1mg/kg with progressive tapering for 6 months. Follow up at 7 months showed no sign of skin, ENT, or kidney relapse with a complete resolution of proteinuria.

**Patient 3**

A 61-year-old female patient with a 7-year prior diagnosis of ANCA negative necrotizing vasculitis with neurological and skin involvement, without IgA deposit, was referred for a COVID-19 infection and relapsing vasculitis. She presented with a paucisymptomatic SARS-CoV-2 infection with fever and diarrhea and was not vaccinated. The time between the COVID-19 infection 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 creatininemia of 169 µmol/l, an albuminemia of 28g/l, a microscopic haematuria and a proteinuria measured at 0.7 g/24h, 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 extra-capillary proliferation.

At first line, regimen, treatment with prednisone 1mg/kg/day was started and was complicated after 3 days by a Campylobacter jejuni and Klebsiella oxytoca colitis, and a sacral eschar. Glucocorticoids were suspended after 21 days due to uncontrolled cutaneous complications of the sacral eschar. At 3 months after glucocorticoids suspension, a cutaneous relapse occurred, and prednisone was re-introduced at 1mg/kg/day. At 3 weeks after the resumption of glucocorticoids, due to behavioural and phasic disorders with insomnia, it was decided to quickly taper them for one month and introduce mycophenolate mofetil. Finally, three weeks after, it was decided to switch to azathioprine 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 while no vaccine was available at the time. The time between the COVID-19 infection 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, the creatininemia was at 65 µmol/l with no proteinuria or microscopic haematuria. IgA count wasn’t available. Histological analysis of skin biopsy showed leukocytoclastic vasculitis and IgA deposits in cutaneous vessels. No treatment was initiated, and 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 vaccine without need of specific treatment.

Patient 5

A 52-year-old female patient, with no prior comorbidities was referred for COVID-19 infection with vascular purpura and abdominal pain. She presented with a low flow O2 therapy requiring SARS-CoV-2 infection with no vaccination available at that time. The time between the COVID-19 and the first symptoms of IgAV was 13 days. First manifestations were vascular purpura of the lower limbs and abdominal pain. The baseline CRP was 60 mg/l, with
creatininemia of 43 µmol/l without proteinuria or microscopic haematuria. IgA count wasn’t available.

Histological analysis of skin biopsy found leukocytoclastic vasculitis and IgA deposits in cutaneous vessels. Abdominal CT showed a parietal thickness with sub mucosal oedema and segmentary damages and the eso-gastro-duodenal endoscopy didn’t reveal any histological signs of vasculitis abnormalities.

Given the abdominal involvement, it was decided to administer intravenous pulses of 250 mg of methylprednisolone for 3 consecutive days relayed by glucocorticoids 1mg/kg/day and gradually tapered. Follow up to 9 months showed no sign of relapse.

All main demographic and clinical patients’ characteristics are summarized in table 1.

4. Discussion

Herein, we reported the first case series of 5 IgAV patients closely following COVID-19. Nowadays, there are robust arguments linking IgAV to infections, particularly 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 damages (12). SARS-CoV-2 may be responsible for the so called “cytokine storms” including increased IL-6 production (13,14). In view of the respiratory tract involvement, the cytokine storm in some COVID-19 patients taken together with the 22 million peoples infected in the country (15), we could have expected an increase in the number of IgAV during the pandemic. On the contrary, according to our data and the literature, it seems to remain a very rare disease.

To our knowledge, 14 cases have been reported so far, excluding ours, and 6 of them were observed in children (16–18). In our series, median age was 45y as that was reported in the adults’ cases from the literature. In the previously reported cases, the COVID 19 infection was mostly not severe and did not require oxygen therapy. Only 3 cases of severe infection were reported. The 3 of them requiring hydroxychloroquine, lopinavir/ritonavir, two were treated in association with tocilizumab, and one needed continuous positive airway pressure (19–21). The baseline manifestations of vasculitis in our study agree with those reported in the literature. Five adults patients (62.5%) were treated with glucocorticoids in the literature specifically for the vasculitis symptoms, one of them in combination with rituximab for a rapid deterioration.
of renal function as compared to 4 (80%) in our cohort (19). The data regarding progression seem rather reassuring both in our cohort and literature, even if follow-up was short. Only one of our patients had received the Bnt162b2 COVID-19 vaccination (one data missing) experiencing a moderate skin relapse after the first one which is not sufficient to form any conclusions or recommendations.

Understanding why there is so few IgAV following SARS-CoV-2 infection reported would require further epidemiological and experimental studies. The systematic 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 don’t explain the scarce case report of IgAV following COVID-19 infection.

Of course, the total number of IgAV following SARS-CoV-2 infection cases around the world is not known. Our work make it impossible to establish the true incidence of the French IgAV following SARS-CoV-2 infection over the studied period, and we also did not include paediatric forms. However, IgAV are histologically confirmed in all our observations, which was not necessarily the case in all observations reported in the literature. All COVID-19 infections were documented with a four-week delay before the onset of IgAV that seemed to us to be a fair balance to maintain a reasonable presumption of imputability. Additionally, all our cases, except maybe for one (patient 2), are de novo IgAV regarding the absence in their past medical history, of vasculitis rash, arthritis, or renal involvement.

The progression of IgAV following COVID-19 infection remains reassuring and it is interesting to note that in the literature or in our cohort, respectively 3 patients (43%) and 2 patients (40%) presented a comorbidity such as cirrhosis or regular alcohol consumption (19), an underlying autoimmune disease (22) which for some may be factors favouring the occurrence of IgAV (23).

5. Conclusion

Despite the small number of cases reported here, the outcome of patients with IgAV following SARS-CoV-2 infection appears favourable. In most of our patients, the SARS-CoV-2 infection was pauci-symptomatic, prompting an RT-PCR test to look for COVID-19 infection in patient without any evident trigger of IgAV.
6. Bibliography


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<th>Comorbidities</th>
<th>COVID 19 symptoms</th>
<th>Initial Organs involvement</th>
<th>Initial Biological parameters</th>
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<tbody>
<tr>
<td>Patient 1</td>
<td>M/57</td>
<td>2</td>
<td>Alcoholic and metabolic cirrhosis</td>
<td>Paucisymptomatic (cough, fever, asthenia)</td>
<td>Vascular purpura of the upper and lower limbs and abdomen. Arthritis in the ankles and knees. Abdominal pain and ileitis. Kidney involvement (non-proliferative IgA nephropathy)</td>
<td>CRP 15.1 mg/l. Creatininemia : 67µmol/l. Proteinuria 2.7 g/24h IgA : 7.19 g/l</td>
<td>Intravenous methylprednisolone (x3) relayed by glucocorticoids 1mg/kg. No specific COVID 19 treatment.</td>
<td>At 4 months after hospital discharge: Aggravated proteinuria at 6g/24h, with creatininemia at 108µmol/l. No abdominal pain, no skin involvement</td>
<td>No new vaccination</td>
<td>6 months</td>
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<td>Patient 2</td>
<td>F/41</td>
<td>0</td>
<td>No comorbidities</td>
<td>Paucisymptomatic (cough, fever, asthenia)</td>
<td>Vascular purpura of the lower limbs. Arthritis in the elbows, ankles, and right knee. Kidney involvement with nephrotic syndrome (non-proliferative IgA nephropathy)</td>
<td>CRP: 225mg/l Creatininemia: 41 µmol/l. Proteinuria : 3.7 g/24h. IgA : 1.71 g/l</td>
<td>Intravenous methylprednisolone (x5) relayed by Glucocorticoids 1mg/kg. No specific COVID 19 treatment.</td>
<td>No relapse</td>
<td>No relapse</td>
<td>7 months</td>
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<td>Case Study 1</td>
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<td>Four-year prior diagnosis of necrotising vasculitis, with ANCA negativity treated by cyclophosphamide and azathioprine</td>
<td>Paucisymptomatic (fever, diarrhea)</td>
<td>Vascular purpura of the upper and lower limbs. Kidney involvement (non-proliferative IgA nephropathy)</td>
<td>CRP: 135 mg/l Creatininemia: 169 µmol/l. Proteinuria: 0.7 g/24 h IgA: No information</td>
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<td>Glucocorticoids 1 mg/kg.</td>
<td>Prednisone discontinuation at 3 weeks due to uncontrolled cutaneous complications of the sacral eschar. Cutaneous relapse at 3 month without treatment: reintroduction of prednisone 1 mg/kg/day with psychiatric sides effects at 3 weeks. Introduction of mycophenolate mofetil. Skin relapse at 3 weeks after mycophenolate mofetil introduction with new psychiatric effects at 4 months.</td>
<td>No vaccination</td>
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manifestation and switch to azathioprine and colchicine.
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Comorbidities</th>
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<th>Skin relapse</th>
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<td>4</td>
<td>F/24</td>
<td>No</td>
<td>Paucisymptomatic (cough, fever, asthenia)</td>
<td>Vascular purpura of the upper and lower limbs. Ankle arthralgia.</td>
<td>CRP: No information Creatininemia: 65 µmol/l. Proteinuria: negative IgA: No information</td>
<td>No treatment</td>
<td>Persistent skin relapses after 6 and 12 months.</td>
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<td>5</td>
<td>F/52</td>
<td>No</td>
<td>Dyspnea with O2 therapy for 48 hours à 1l/min.</td>
<td>Vascular purpura of the upper and lower limbs. Abdominal pain with parietal thickness and oedema without ileitis.</td>
<td>CRP: 60 mg/l Creatininemia: 43 µmol/l. Proteinuria: negative IgA: No information</td>
<td>Intravenous methylprednisolone (x3) relayed by Glucocorticoids 1mg/kg. No specific COVID-19 treatment.</td>
<td>No relapse</td>
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</table>

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

Age is given in years.

*Abbreviations: M, male; F, Female; IgA, immunoglobulin A; IgAV, IgA vasculitis; CRP, C-reactive protein; ENT, Ear, Nose, Throat.*