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CASE BASED REVIEW

Vasculitis flare after COVID-19: report of two cases in patients with preexistent controlled IgA vasculitis and review of the literature

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Abstract

COVID-19 has been related to several autoimmune diseases, triggering the appearance of autoantibodies and endothelial dysfunction. Current evidence has drawn attention to vasculitis-like phenomena and leukocytoclastic vasculitis in some COVID-19 patients. Moreover, it has been hypothesized that COVID-19 could induce flares of preexisting autoimmune disorders. Here, we present two patients with previously controlled IgA vasculitis who developed a renal and cutaneous flare of vasculitis after mild COVID-19, one of them with new-onset ANCA vasculitis. These patients were treated with glucocorticoids and immunosuppressants achieving successful response. We also provide a focused literature review and conclude that COVID-19 may be associated with triggering of vasculitis and could induce flares of previous autoimmune diseases.

Keywords Vasculitis · COVID-19 · Autoimmune diseases · Flare · ANCA-associated vasculitis

Introduction

Novel severe acute respiratory syndrome by coronavirus-2 (SARS-CoV-2) disease (COVID-19) ranges from asymptomatic to severe cases, which are characterized by a severe acute respiratory syndrome. Even mild forms of COVID-19 have been associated with various autoimmune manifestations and accordingly this infection has been proposed as a trigger of several autoimmune diseases [1]. Molecular mimicry and hyperinflammation due to hyperstimulation of the immune system seem to be the potential mechanisms of autoimmunity in COVID-19 [2] and may lead to the appearance of previously non-existent autoantibodies [3]. Furthermore, complement activation in COVID-19 has been shown to activate platelets and neutrophil extracellular traps (NETs) [1, 4] involved in multiple autoimmune diseases [3].

A study conducted in China in patients with critical SARS-CoV-2 pneumonia showed a 50% prevalence of antinuclear antibodies [5] and another study found anti-neutrophil cytoplasmic antibodies (ANCA) in 13% of these patients [6]. Other studies showed an increased incidence of positivity for lupus anticoagulant and antiphospholipid antibodies in COVID-19 patients [7].

Furthermore, there are some reports in the literature describing de novo development of autoimmune diseases associated with COVID-19 [2, 3, 8]. Additionally, patients with preexisting autoimmune diseases may undergo reactivation of their disease after SARS-CoV-2 infection; however, the evidence in the literature about this process is limited. Herein, we report two cases of reactivation of IgA vasculitis after COVID-19 infection.

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Case presentation

Case 1

A 27-year-old white male was admitted to our rheumatology department in January 2021 presenting with diffuse arthralgias and cutaneous purpuric lesions in the upper and lower limbs. The patient had been diagnosed with Henoch–Schönlein purpura 3 years earlier, but had no other medical history of interest. At diagnosis, the patient had cutaneous purpura, articular and renal disease (mesangial proliferative glomerulonephritis with IgA deposits). He was successfully treated with oral glucocorticoids for 1 year achieving sustained remission without subsequent relapses.

In our assessment, physical examination revealed generalized palpable purpura distributed over all the extremities, gluteal region and abdomen, without evidence of arthritis, gastrointestinal symptoms or associated fever. A month before, the patient had suffered an asymptomatic SARS-CoV-2 infection diagnosed by positive real-time polymerase chain reaction (RT-PCR) test in nasopharyngeal swab sample, which was indicated due to close contact with a COVID-19-positive subject.

Laboratory results showed normal full blood count, liver and renal function tests, as well as normal coagulation profile, erythrocyte sedimentation rate and C-reactive protein values. Serum IgA levels were increased (357 g/L), while IgG and IgM were normal and the rest of the autoimmune assays, including ANCAs, were negative. Urinalysis was normal.

Given the suspicion of an IgA vasculitis flare, a skin purpuric lesion was biopsied, showing histological results consistent with leukocytoclastic vasculitis. Immunofluorescence microscopy demonstrated predominant IgA deposition thereby confirming IgA vasculitis relapse. The patient received 50 mg/day of prednisone with improvement of purpuric lesions. Three months later, the patient developed microhematuria, with adequate renal function, which was resolved by treatment with azathioprine at a dose of 1.5 mg/kg/day.

Case 2

A 62-year-old Hispanic woman presented to our department with purpuric lesions in the upper limbs with no other associated symptoms. She had been diagnosed with IgA vasculitis four years before, which consisted of anterior scleritis, joint and cutaneous involvement with positive skin biopsy at two different times (immunofluorescence-confirmed leukocytoclastic vasculitis with IgA deposition). ANCA antibodies were negative and C3 decrease was observed, consistent with hypocomplementemic IgA vasculitis. Treatment with high doses of glucocorticoids and methotrexate was enough to achieve remission, which was maintained after glucocorticoid withdrawal under methotrexate monotherapy.

In March 2020, the patient presented symptoms suggestive of SARS-CoV-2 infection, but did not require admission and recovered remaining isolated at home. She then tested positive for IgG COVID-19 antibodies in the next month. Three months later, the patient advanced her scheduled appointment to our clinic. Physical examination revealed a palpable purpura on arms, without signs of arthritis. She was afebrile and her pulse and blood pressure were normal. Laboratory results revealed a reduction in glomerular filtration rate (49 ml/min/1.73 m^2 vs previous of 90 ml/min/1.73 m^2), mild anemia and lymphopenia with normal acute phase reactants. Urinalysis showed microhematuria and proteinuria up to 1.4 g/24 h. ANCA determination tested positive for proteinase 3 (anti-PR3) antibodies (459 IU/ml, normal upper limit 20 IU/ml) with low complement levels of C3.

A percutaneous renal biopsy was performed showing findings of rapidly progressive glomerulonephritis with fibroepithelial crescents compatible with a diagnosis of ANCA-associated vasculitis. The patient was treated with 3 methylprednisolone boluses of 500 mg/day and intravenous rituximab (4 weekly doses of 375 mg/m^2) as induction therapy, followed by oral prednisone 1 mg/kg/day. After 3 months, renal function was partially recovered, proteinuria and ANCA levels were notably reduced and cutaneous lesions were improved. Currently, the patient remains with 10 mg of oral prednisone and rituximab.

Search strategy and case selection

A literature review was performed to identify studies focused on the development of ANCA vasculitis or IgA vasculitis after COVID-19. Accordingly, MEDLINE database was accessed through PubMed and searched for articles published in English or Spanish between March 2020 and October 2021. The search strategy used the following key terms related to vasculitis and COVID-19: ("IgA vasculitis" OR "Henoch–Schönlein purpura" OR "ANCA vasculitis" OR "granulomatosis with polyangiitis" OR "microscopic polyangiitis") AND ("COVID-19" OR "SARS-CoV-2" OR "coronavirus"). Search strategy is represented in Fig. 1. We selected only patients with confirmed positive test for COVID-19 by serology or RT-PCR in nasopharyngeal swab. Cases with insufficient information to confirm the diagnosis of IgA vasculitis or ANCA vasculitis (positive biopsy, positive ANCA or increase of IgA levels) were not considered. To capture all the available literature, articles were selected

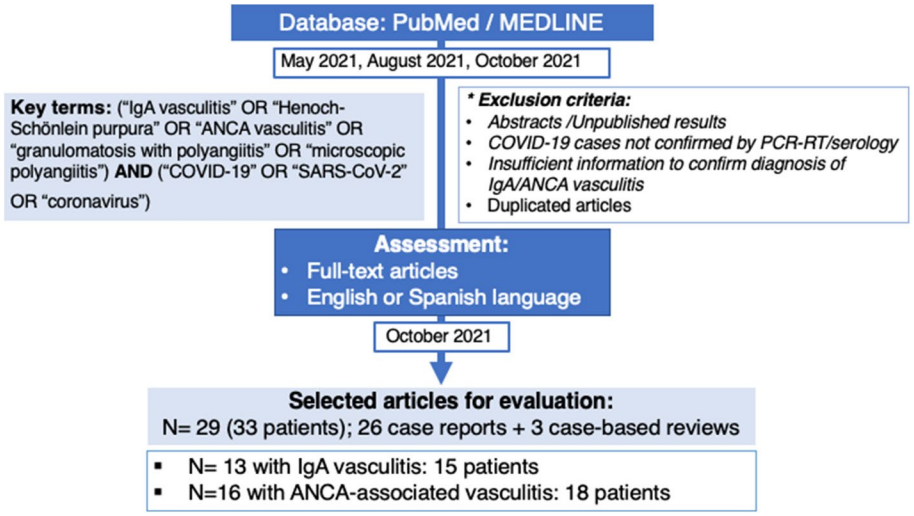

Fig. 1 Flowchart of the bibliographic search strategy and selection criteria. *ANCA* antineutrophil cytoplasmic antibodies, *COVID-19* coronavirus disease 2019, *RT-PCR* reverse transcription polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2

with no filter in terms of design, included case reports and case series, and with no limits in the age of the patients. Abstracts or not published results were not included. This search strategy was applied at three different times (May 2021, August 2021 and October 2021) covering until October 25th 2021. Finally, a total of 29 articles were selected for evaluation.

Results

We identified 16 reports describing 18 cases (12 women/6 men) of new-onset ANCA-associated vasculitis in COVID-19 patients and presumably related to this disease [8–23]. The main characteristics of these cases are presented in Table 1. In eight cases the onset of ANCA vasculitis coincided with the infection, six of them had pneumonia. Of the 18 cases, 16 presented organ-threatening disease: 13 patients presented renal involvement (pauci-immune glomerulonephritis) and 11 patients had diffuse alveolar hemorrhage, in 9 of these patients both diseases coexisted. Three patients also presented pulmonary involvement, pulmonary nodules with cavitary lesions in two patients and hyper eosinophilic bronchiolitis in one patient. Only seven patients had leukocytoclastic vasculitis and two patients had arthritis.

Regarding the type of ANCA, anti-MPO antibodies were more frequently detected than anti-PR3 antibodies (nine and seven patients, respectively). All patients received steroids and most cases were treated with immunosuppressive combined therapy: nine with rituximab, nine with plasmapheresis, six with cyclophosphamide (CYC), two with intravenous immunoglobulins (IVIG), one with mycophenolate mofetil (MMF) and the other one with azathioprine. In the follow-up, most patients responded well to glucocorticoids and immunosuppressive agents but two patients died as a result of the disease (both with diffuse alveolar hemorrhage) [10, 20]. Another patient died as a consequence of multiple infections [23]. Notably, three of these cases had a preexistent autoimmune disease [12, 13, 23]. Another case simultaneously developed an antiphospholipid syndrome [18].

Concerning IgA vasculitis related to COVID-19, 15 cases (12 men; 3 women) in 13 reports have been published to date [24–36], which are summarized in Table 2. Half of the cases were diagnosed in childhood. These cases presented new-onset IgA vasculitis, most of them with palpable purpura (13 patients) and 8 patients developed renal disease (IgA nephropathy). Additionally, eight patients presented with gastrointestinal involvement and three patients presented with arthritis. In eight patients, the onset of vasculitis coincided with the infection. All of these patients were treated with glucocorticoids and four patients received immunosuppressants for renal involvement (1 rituximab, 2 MMF, 1 CYC) with favorable renal response in all cases [25, 30, 36]. No deaths were identified.

Discussion

COVID-19 is bringing back many aspects of autoimmune diseases that seemed forgotten. Indeed, SARS-CoV-2 infection could break self-tolerance and trigger systemic autoimmunity. Several reports have suggested that COVID-19 may be followed by immune activation and the development of several autoimmune manifestations [2, 3, 37]; however, there is currently a lack of robust evidence supporting SARS-CoV-2 as the causal trigger of these phenomena [38].

Although the association between COVID-19 and the relapse of vasculitis found in our cases cannot be fully demonstrated and could be incidental, the chronology of events suggests a potential role of the viral infection on the onset of both vasculitis flares. Indeed, other viruses have been proposed as a trigger of vasculitis based on molecular mimicry,

Table 1 Reported cases of ANCA-associated vasculitis related to COVID-19

Author [ref.] diagnosis	Age (years); sex (M/F)	Medical history	COVID-19 symptoms (diagnosis); time to vasculitis onset	Clinical manifestations	Type of ANCA	Non-GC immuno-modulators and biological therapies	Outcome
Uppal et al. [8]	64; M	Previous cryptogenic organizing pneumonia	Pneumonia (RT-PCR +); concomitant	Glomerulonephritis	P-ANCA: Anti-MPO	Rituximab	Partial renal response
Uppal et al. [8]	46; M	Diabetes mellitus	Pneumonia (RT-PCR +); concomitant	Glomerulonephritis and leukocytoclastic vasculitis	Anti-PR3	Rituximab	Complete response
Moeinzadeh et al. [9]	25; M	None	Asymptomatic (RT-PCR +); concomitant	Glomerulonephritis and diffuse alveolar hemorrhage	C-ANCA	CYC Plasmapheresis IVIG	Partial renal response with stable creatinine Complete pulmonary improvement
Hussein et al. [10]	37; F	None	Asymptomatic (RT-PCR +); concomitant	Diffuse alveolar hemorrhage and arthritis	C-ANCA: Anti-PR3	IVIG Plasmapheresis	Death
Selvaraj et al. [11]	60; F	Diabetes mellitus, allergic rhinitis	Upper respiratory tract symptoms and myopericarditis (RT-PCR +); 4 wks	Glomerulonephritis and diffuse alveolar hemorrhage	C-ANCA: Anti-PR3	Rituximab Plasmapheresis	Partial pulmonary and renal response
Jalalzadeh et al. [12]	48; F	Diabetes mellitus and scleroderma	Asymptomatic (RT-PCR); 5 wks	Glomerulonephritis and diffuse alveolar hemorrhage	P-ANCA: Anti-MPO	Rituximab	Unknown
Singh et al. [13]	46; F	Rheumatoid arthritis, hypertension	Upper respiratory tract symptoms (RT-PCR +); 6 wks	Glomerulonephritis and diffuse alveolar hemorrhage	P-ANCA: Anti-MPO	Rituximab	Remission
Powell et al. [14]	12; F	None	Asymptomatic (IgG serology +); unknown	Glomerulonephritis and diffuse alveolar hemorrhage	P-ANCA: Anti-MPO	Rituximab CYC	Improvement in clinical status
Merveilleux du Vignaux et al. [15]	59; F	HBV chronic infection, Asthma	Upper respiratory tract symptoms (RT-PCR +); 4 wks	Hypereosinophilic bronchiolitis and leukocytoclastic vasculitis	Anti-MPO	Azathioprine	Favorable outcome
Izci Duran et al. [16]	26; M	None	Pneumonia (RT-PCR +); concomitant	Glomerulonephritis and diffuse alveolar hemorrhage	P-ANCA: Anti-MPO	CYC Plasmapheresis	Lung findings regressed Hemodialysis was continued after 2 doses of cyclophosphamide
Izci Duran et al. [16]	36; F	None	Upper respiratory tract symptoms (RT-PCR +); few weeks	Glomerulonephritis and cavitary lung lesions	Anti-PR3	CYC	Renal improvement
Reiff et al. [17]	17; M	None	Pneumonia (RT-PCR +); concomitant	Pulmonary nodules with cavitary lesions and fever	C-ANCA Anti-PR3	Rituximab	Asymptomatic status and significant improvement in nodules size
Maritati et al. [18]	64; F	Hypertension	Pneumonia (RT-PCR +); concomitant	Glomerulonephritis and antiphospholipid syndrome	Anti-PR3	CYC Plasmapheresis Rituximab	Renal function gradually ameliorated with stable creatinine

Table 1 (continued)

Author [ref.] diagnosis	Age (years); sex (M/F)	Medical history	COVID-19 symptoms (diagnosis); time to vasculitis onset	Clinical manifestations	Type of ANCA	Non-GC immuno-modulators and biological therapies	Outcome
Lind et al. [19]	40; M	None	Upper respiratory tract symptoms (RT-PCR +); 10 days	Glomerulonephritis, diffuse alveolar hemorrhage and arthritis	C-ANCA: Anti-PR3	Rituximab	The patient continued to improve clinically in the months following discharge
Patel et al. [20]	77; F	Hypertension, dyslipidemia, diabetes mellitus	Upper respiratory tract symptoms; 6 wks	Diffuse alveolar hemorrhage	Anti-MPO	Plasmapheresis	Death
Allena et al. [21]	60; F	Coronary artery disease, asthma, hypertension, dyslipidemia	Unknown; 4 wks	Glomerulonephritis and diffuse alveolar hemorrhage	Anti-MPO	Plasmapheresis Rituximab	Pulmonary and renal improvement
Fireizen et al. [22]	17; M	Obesity, asthma	Pneumonia (RT-PCR); 2 months	Diffuse alveolar hemorrhage and glomerulonephritis	P-ANCA Anti-MPO	Plasmapheresis CYC	Complete response
Mashinchi et al. [23]	21; F	SLE	Pneumonia (RT-PCR); concomitant	Glomerulonephritis with a flare of SLE (malar rash, oral ulcers, arthralgia)	C-ANCA	Plasmapheresis MMF, CYC	Death
Current case	62; F	Previous IgA vasculitis	Upper respiratory symptoms; 3 months	Glomerulonephritis with palpable purpura	C-ANCA Anti-PR3	Rituximab	Complete response

ANCA anti-neutrophil cytoplasmic antibodies, *COVID-19* coronavirus disease 2019, *CYC* cyclophosphamide, *Anti-MPO* anti-myeloperoxidase antibodies, *Anti-PR3* anti-proteinase 3 antibodies, *F* female, *GC* glucocorticoids, *HBV* hepatitis B virus, *IVIG* intravenous immunoglobulins, *M*, male, *MMF* mycophenolate mofetil, *RT-PCR* reverse transcription polymerase chain reaction, *SLE* systemic lupus erythematosus, *wks* weeks

Table 2 Reported cases of IgA vasculitis related to COVID-19

Case	Age (years); sex (M/F)	Medical history	COVID-19 symptoms (diagnosis); time to vasculitis onset	Clinical characteristics	Non-GC immuno-modulators and biological therapies	Outcome follow-up
Li et al. [24]	30; M	None	Upper respiratory tract symptoms (RT-PCR +); concomitant	Leukocytoclastic vasculitis, IgA nephropathy, abdominal pain and arthralgia	None	Asymptomatic. Preserved renal function and dramatically reduced proteinuria
Suso et al. [25]	78; M	Hypertension, dyslipidemia, aortic valve stenosis, and bladder cancer in remission	Pneumonia (RT-PCR +); 3 weeks	Leukocytoclastic vasculitis, IgA nephropathy, and arthritis	Rituximab	On discharge, serum creatinine had improved, but the patient persisted with proteinuria and hematuria. Cutaneous purpura markedly improved
Hoskins et al. [26]	2; M	None	Asymptomatic (RT-PCR +); concomitant	Leukocytoclastic vasculitis with IgA deposits, abdominal pain and hematochezia	None	Complete resolution of skin findings; abdominal symptoms also resolved
Allez et al. [27]	24; M	Crohn's disease	Asymptomatic (RT-PCR +); concomitant	Leukocytoclastic vasculitis with IgA deposits, abdominal pain and arthritis	None	Unknown
Barbetta et al. [28]	62; M	None	Pneumonia (RT-PCR +); 10 days	Leukocytoclastic vasculitis with IgA deposits, IgA nephropathy, abdominal pain and hematochezia	None	Improvement of renal function and progressive remission of abdominal pain and skin purpura
AlGhoozi et al. [29]	4; M	None	Upper respiratory tract symptoms; (RT-PCR +); 5 weeks	Palpable purpura and arthralgia	None	At one week the rash was still present bilaterally, but he had remained pain free
Sandhu et al. [30]	22; M	None	Asymptomatic (RT-PCR +); concomitant	Leukocytoclastic vasculitis, arthritis, IgA nephropathy, abdominal pain and vomiting	Mycophenolate mofetil	Cutaneous lesions, joint involvement and abdominal symptoms resolved, urinalysis normalized after 2 weeks
Jacobi et al. [31]	3; M	Corrected Hirschsprung disease	Asymptomatic (RT-PCR +); concomitant	Palpable purpura and abdominal pain	None	Abdominal pain responded well to glucocorticoids on discharge
Huang et al. [32]	65; F	Hypertension	Pneumonia (RT-PCR +); concomitant	IgA nephropathy	None	Asymptomatic 3 months later, eGFR normal, UACR 33.61 mg/g
El Hasbani et al. [33]	16; M	None	Upper respiratory tract symptoms (RT-PCR +); concomitant	Palpable purpura, abdominal pain and hematochezia	None	Rapid clinical improvement
Nakandakari et al. [34]	4; F	None	Upper respiratory tract symptoms (IgM/ IgG +); 8 days	Palpable purpura, abdominal pain and hematochezia	None	Progressive decrease in abdominal pain and purpuric lesions
Falou et al. [35]	8; M	None	Asymptomatic (RT-PCR +); concomitant	Palpable purpura	None	Rash and ankle pain resolved

Table 2 (continued)

Case	Age (years); sex (M/F)	Medical history	COVID-19 symptoms (diagnosis); time to vasculitis onset	Clinical characteristics	Non-GC immuno-modulators and biological therapies	Outcome follow-up
Oñate et al. [36]	87; M	Hypertensive cardiomyopathy	Upper respiratory tract symptoms (IgG+); 2 months	Leukocytoclastic vasculitis with IgA deposits and nephropathy (without biopsy)	None	At 5 months of follow-up, he had complete recovery of renal function
Oñate et al. [36]	64; F	Hypertension, CKD	Pneumonia (RT-PCR+); 9 months	IgA nephropathy	Cyclophosphamide	At 4 months of follow-up, the patient had improvement in renal function and reduced proteinuria
Oñate et al. [36]	84; M	Hypertension, dyslipidemia, COPD, CHF	Pneumonia (RT-PCR+); concomitant	Palpable purpura and IgA nephropathy	Mycophenolate mofetil	At 10 months of follow-up, the patient partially recovered kidney function with negative proteinuria and maintains microhematuria
Current case	27; M	Previous IgA vasculitis	Asymptomatic (RT-PCR+); 4–5 weeks	Flare of IgA vasculitis (palpable purpura, arthralgia and IgA nephropathy)	Azathioprine	Complete cutaneous and renal response

COPD chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *COVID-19* coronavirus disease 2019, *CHF* congestive heart failure, *eGFR* glomerular filtration rate, *F* female, *GC* glucocorticoids, *M* male, *RT-PCR* reverse transcription polymerase chain reaction, *UACR* urine albumin-to-creatinine ratio

tropism for vascular endothelium, immune complex deposition within the vessel walls and autoantibody production [39–41]. Causal relationships have been well established between hepatitis C virus and cryoglobulinemic vasculitis and between hepatitis B virus and polyarteritis nodosa [39, 40].

Current evidence supports that the mechanisms involved in SARS-CoV-2 regulation of autoantibody generation, endothelial inflammation and dysfunction, complement activation and NET production may lead to vasculitis [1–4]. Vasculitis-like phenomena during COVID-19 infection have been described in the literature and numerous reports have described cutaneous vascular lesions in COVID-19 patients [37, 42]. Therefore, some authors suggest that virus–host interactions may lead to both direct and indirect microvasculature damage through endothelial cell inflammation [42]. Additionally, thrombosis, lymphocytic endothelitis, and apoptotic bodies have been found in COVID-19 autopsies [37, 42]. Furthermore, several studies have reported the presence of leukocytoclastic vasculitis in cutaneous biopsies from COVID-19 patients obtained during the active or convalescent phases of this infection [43–45].

We present two cases of patients with prior history of IgA vasculitis with ocular, renal, skin and articular involvement, both of them in sustained remission, who developed a new flare of vasculitis shortly after SARS-CoV-2 infection. One case suffered mild COVID-19, while the other remained asymptomatic.

Case 1 had a relapse of the disease with hematuria, arthralgia and cutaneous flare and the second case presented with cutaneous and renal disease consistent with ANCA-associated vasculitis. The absence of ANCA in the patient´s previous history, along with C3 consumption in a well-documented IgA vasculitis prompted us to consider a newly induced ANCA-associated vasculitis; however, recurrent low C3 levels pointed to a relapse of a hypocomplementemic IgA vasculitis, likely in the context of an overlapping vasculitis. We cannot definitely rule out that both entities were present prior COVID19 infection, as ANCA levels were not systematically analyzed during remission at subsequent follow-up.

Our two patients suffered severe manifestations of vasculitis (kidney involvement in both patients). This finding was also described in the reported cases of vasculitis related to COVID-19: renal disease was reported in 15/18 patients with ANCA vasculitis and in 8/15 patients with IgA vasculitis. In line with our findings, the reviewed cases of post-COVID-19 ANCA vasculitis were more severe and with a worse prognosis than those with IgA vasculitis, showing organ-threatening disease in 88% of the cases (16/18) and three deaths. Both renal and pulmonary involvement were very common in ANCA-associated vasculitis. In addition, the reported cases showed a predominance of IgA vasculitis in males and ANCA-associated vasculitis in females.

Current evidence on flares of preexisting autoimmune diseases in COVID-19 patients is very limited. Flares of SLE in patients with COVID-19 have been described [46]. A study in a cohort of Hispanic COVID-19 patients from United States with rheumatic diseases identified COVID-19 positivity as a risk factor for disease flares [47]. To date, we have not found publications reporting cases of relapses of previous controlled IgA vasculitis associated with COVID-19.

Furthermore, to the best of our knowledge, there are no descriptions in the literature of flares of vasculitic diseases associated with COVID-19. Therefore, our cases provide valuable information supporting the novel hypothesis that COVID-19 could act as an immune trigger for vasculitis contributing to flares of prior disease, even with new autoantibody-induced manifestations.

Conclusion

COVID-19 infection could be associated with vasculitis triggering and could induce flares of previous autoimmune diseases. To our knowledge, this is the first description of vasculitis reactivation following COVID-19 infection in patients with preexisting IgA vasculitis. These findings suggest a causal relationship between COVID-19 and vasculitis, although further research is needed to establish solid evidence about this subject.

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Declarations

Conflict of interest Cristina Valero, Juan Pablo Baldivieso-Achá, Miren Uriarte, Esther F. Vicente-Rabaneda, Santos Castañeda and Rosario Garcia Vicuña declare that they have no conflict of interest related to the work submitted for publication.

Ethics statement The patients of the two cases were fully informed, and we obtained signed informed consent to report their case.

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