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COVID-19 and New Onset IgA Vasculitis: A Systematic Review of Case Reports

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Contribution to Emergency Nursing Practice

- The current literature on immunoglobulin A vasculitis indicates that it may be triggered by upper respiratory tract infections. Cases of COVID-19–mediated immunoglobulin A vasculitis are characterized by a more severe disease course because of increased renal involvement.
- This article contributes the finding that existing literature suggests immunoglobulin A vasculitis may result from COVID-19 infections and that prompt recognition and treatment are necessary to improve patient outcomes.
- Key implications for emergency nursing practice found in this manuscript are being aware that COVID-19 is a provoking factor that may lead to the development of immunoglobulin A–related disorders. In addition, the manuscript outlines management and treatment for patients diagnosed with immunoglobulin A vasculitis.

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J Emerg Nurs 2022;48:348-65.
Available online 13 May 2022
0099-1767

https://doi.org/10.1016/j.jen.2022.05.002

Abstract

Introduction: Immunoglobulin A vasculitis is historically more commonly found in children after certain viral infections such as Epstein-Barr, varicella virus, and parvovirus B19. COVID-19 has not been formally established in literature as a trigger for immunoglobulin A vasculitis. However, a main pathogenetic mechanism of COVID-19 is vascular damage, which makes it likely that vasculitis associated with COVID-19 (ie, COVID-19–mediated immunoglobulin A vasculitis) could be biologically plausible, with serious implications, especially for adults. The purpose of this review is to assist emergency nurses in gaining knowledge on the pathophysiology, symptoms, and treatment of COVID-19–mediated immunoglobulin A vasculitis.

Methods: A systematic search for case reports of COVID-19–associated immunoglobulin A vasculitis was conducted in the PubMed and Scopus electronic databases. The search terms used were COVID-19, coronavirus 2019, SARS COVID-19, and IgA vasculitis, case reports. The following were the inclusion criteria: publication dates between December 1, 2019, and December 1, 2021; full-text article, clinical case studies, and letters to the editor available electronically in English. The following were exclusion criteria: a summary of reports and newspaper publications.

Results: Only 13 clinical cases met the inclusion criteria. The median age of patients described in the case reports were 38.1 years. Of them, 3 children were less than 5 years old. Twelve patients were male. In 7 of 13 cases of immunoglobulin A vasculitis, renal involvement was found.

Discussion: The analysis of published clinical cases showed that COVID-19–associated immunoglobulin A vasculitis affected mostly adults and was characterized by a more severe course because of renal involvement. COVID-19 may be a possible trigger for immunoglobulin A–related disorders. More research is needed to better understand the relationship between immunoglobulin A vasculitis and COVID-19.

Key words: IgA vasculitis; COVID-19; Dermatology; Hematology

Introduction

COVID-19 has rapidly spread worldwide, affecting 504 million people and causing more than 6.2 million deaths to date.[1] Typically, patients with COVID-19 present with fever, computed tomography signs of interstitial pneumonia, and respiratory distress; dermatological manifestations of infection have been reported in only a few publications.[2-5] The incidence rate of dermatological manifestations of COVID-19 ranges from 0.2% to 20.4%.[6,7] Immunoglobulin A vasculitis (IgAV) has been identified in previous case reports as a potentially uncommon complication of COVID-19, with no data on its prevalence.

Purpose

The purpose of this systematic review of case reports is to explore the relationship between IgAV and COVID-19 and assist emergency nurses in gaining knowledge on COVID-19–associated IgAV. In this manuscript, we discuss the symptoms and treatment of this condition and review case reports published between December 1, 2019, and December 1, 2021.

Overview of IgA vasculitis

DEFINITION

Vasculitis is a condition that occurs when swelling and inflammation occur to the walls of blood vessels. Vasculitis can occur as a result of autoimmune disorders, infections, and trauma. IgAV is a disease that causes the antibody IgA to collect in small blood vessels, which then experience inflammation and leak blood.[8] The site of vessel involvement, size of the affected vessels, extent of vascular injury, and underlying pathology determine the disease phenotype and severity. IgAV is a leukocytoclastic vasculitis of small vessels with predominant IgA deposition. The exact cause of the illness, however, is unknown. It often occurs after acute respiratory infection (Epstein-Barr, varicella virus, parvovirus B19, Mycoplasma, Campylobacter jejuni).[8,9] IgAV notably affects children between 3 and 15 years. It is estimated that approximately 10% of the affected population are adults and that this category of patients is prone to kidney involvement and malignancy.[10]

PATHOPHYSIOLOGY

The current COVID-19 pandemic has led to a small but growing body of evidence that IgAV may be caused by a viral infection. It is known that COVID-19 can affect the circulatory system and cause apoptosis, inflammation, and dysfunction of endothelial cells and thrombosis.[11] Cutaneous manifestations of COVID-19 include urticaria,[7] reticular rash,[12] red-purple papules,[13] urticarial and varicella-like exanthema,[14,15] petechiae,[16] and even ecchymosis.[17] Moreover, according to some authors, petechiae, purpura, and acral ischemia accompanied by coagulation disorders are prognostically unfavorable symptoms and may indicate a more severe course of the disease.[18] A clinical case of large vessel vasculitis after COVID-19 has been reported recently. The authors suggested that infection and endotheliitis may lead to the development of vasculitis.[19] Exaggerated immune response to COVID-19 leads to IgA accumulation in the vascular wall and renal mesangium and the development of IgAV[20] (Figure 1).

MANIFESTATIONS

Palpable nonthrombocytopenic purpura of lower extremities and buttocks is a characteristic and hallmark sign of IgAV. Other manifestations include acute enteritis, renal impairment, and arthritis. Colicky abdominal pain, abdominal tenderness, and melena are typical gastrointestinal symptoms of IgAV. Intussusception is more common in children. IgAV may occur during the course or before the diagnosis of malignant tumors, particularly with adult-onset IgAV. Adults diagnosed with IgAV are also at a greater risk of kidney involvement.

DIAGNOSTICS

The clinical classification of IgAV is based on research from the European League Against Rheumatism (EULAR), the Paediatric Rheumatology European Society (PRES), and the Paediatric Rheumatology International Trials Organization (PRINTO).[21] Purpura or petechiae must be present, as well as 1 of the other 4 criteria: abdominal discomfort, histopathological appearance, arthralgia, and renal involvement. In addition to the EULAR/PRES/PRINTO clinical criterion for IgAV, histological studies confirming leukocytoclastic vasculitis and IgA deposition in blood vessel walls can be used to confirm the diagnosis. In patients with unusual distribution of rash (extensive lesions or diffusely distributed lesions) and atypical clinical manifestation, tissue biopsy (skin or kidney)

must be done to confirm the clinical diagnosis.[22] Similarly, the absence of IgA staining on biopsy does not rule out the possibility of IgAV.[23]

IgA vasculitis is characterized as vasculitis with IgA1-dominant immune deposits that affect small vessels in the skin and gastrointestinal tract and frequently cause arthritis, according to the 2012 Chapel Hill Consensus Conference.[24] IgAV is also linked to glomerulonephritis, which is indistinguishable from IgA nephropathy (IgAN). Deposition of glomerular IgA on biopsy is characteristic of both IgAV and IgAN. While both IgA nephropathy and IgAV can cause hematuria, IgAV clinically differs from IgA nephropathy in that the pathology includes extra-renal involvement of skin (purpuric rash), joints (arthralgias), and gut (abdominal pain, melena).[24] IgAV is indicated by strong IgA deposition in the absence of other antibody deposition.

MANAGEMENT

IgAV is a self-limiting disease, especially in children. Glucocorticoids are standard treatments in IgAV and are used to reduce inflammation and prevent complications.[22] According to SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative, glucocorticoids should be considered in the presence of the following conditions associated with IgAV: orchitis, cerebral vasculitis, pulmonary hemorrhage and severe gastrointestinal involvement, IgA nephritis, severe abdominal pain, and/or rectal bleeding. The dose of oral glucocorticoids (prednisoLONE/predniSONE) is 1-2 mg/kg/day. In severe cases, intravenous MethylPREDNISolone (eg, 10-30 mg/kg with a maximum of 1 g/day on 3 consecutive days) may be considered.[22]

Additional immune suppressors such as azathioprine, mycophenolate mofetil, and cyclophosphamide are prescribed to patients with more severe cases, including those with renal and gastrointestinal involvement. Although the results of treatment are controversial, a retrospective study by the French Vasculitis Group,[25] as well as a prospective study by Pillebout et al,[26] showed that there is no significant difference between combined treatment of glucocorticoids with immune suppressors (cyclophosphamide) and glucocorticoid treatment alone as it relates to patient outcome and mortality. Recent studies demonstrated the efficiency of riTUXimab, a monoclonal antibody medication, in the treatment of adult-onset IgA vasculitis.[27] Colchicine and dapsone have also been reported to be effective for treating chronic IgA vasculitis. However, there are still no randomized controlled trials to determine the optimal therapeutic dose and duration of treatment.[28] Finally, plasma exchange in combination with steroids has been associated with good outcomes in adults with IgA vasculitis.

Relapses typically occur in 20% to 30% of individuals diagnosed with adult-onset IgA vasculitis. The predictor of relapse was persistent purpura, severe leucocytoclastic vasculitis, abdominal pain, hematuria, and adult onset of the disease.[29]

Method of Identification of Case Reports

We searched PubMed and Scopus databases for articles including case reports published between December 1, 2019, and December 1, 2021, using the following keywords: "COVID-19," "coronavirus 2019," "SARS COVID-2," and "IgA vasculitis." Clinical case studies and letters to the editor that were written in English and accessible in full text were included. Summary reports and newspaper publications were excluded. For inclusion, we independently reviewed the titles and abstracts of retrieved citations, and any inconsistencies were resolved by consensus. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist for writing a systematic review of case reports was used. The quality of clinical cases were evaluated by Equator network's Clinical Case Reporting Guideline Development (CARE) checklist. In total, 680 full-text publications were checked, with reference lists manually scanned for additional studies (See Figure 2).

Discussion of Case Reports

There were only 13 cases that met the requirements for inclusion. In the presented clinical cases, 5 of 13 were found in children. IgAV is more common in children, while COVID-19–associated IgAV is more common in adults (8 cases of 13). Our data are consistent with the results of other study.[30] The analysis of clinical cases showed that COVID-19–associated IgA vasculitis affects mostly adults, and concomitant diseases are characterized by a more severe course of the disease with damage of the skin, joints, and kidneys. Renal involvement was found in 7 of the 13 published clinical cases of IgAV. Renal involvement ranged from proteinuria and/or hematuria to acute renal insufficiency with elevated creatinine. Four of the patients had no respiratory symptoms. It can be assumed that asymptomatic COVID-19 infections in children and young people may cause latent vascular damage. Only 3 patients had

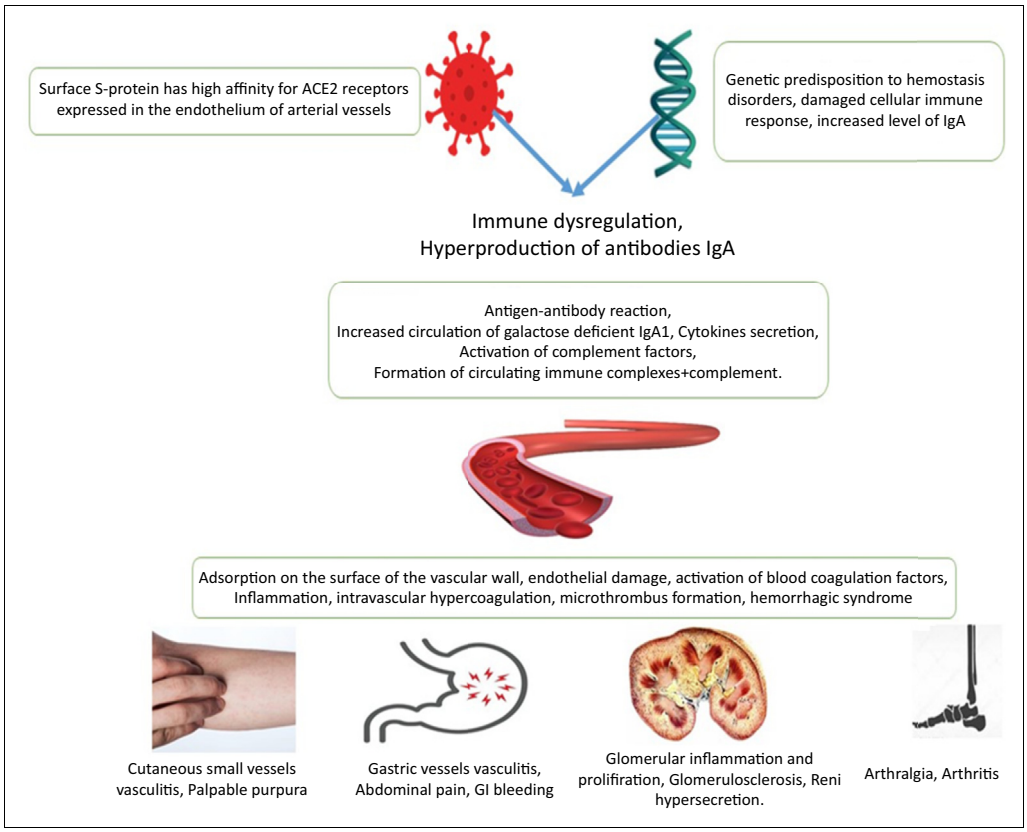

FIGURE 1

Pathogenesis of COVID-19 associated IgA vasculitis. ACE2, angiotensin-converting enzyme 2; IgA, immunoglobulin A; GI, gastrointestinal.

pneumonia. In almost all cases, a positive effect from the use of glucocorticoids was reported, which is similar to the findings of previously reported studies.[31] Only 2 pediatric cases did not require treatment with glucocorticoids.

ADULT CASES

One of the first studies that described COVID-19–related IgAV was published by Allez et al[32] in November 2020 (Tables 1 and 2). This study involved a 24-year-old man with Crohn's disease under anti-TNF therapy and showed skin, joint, and abdominal symptoms of IgAV. A similar case was also described in a 22-year-old young man but with the development of IgA nephritis.[33] Nasopharyngeal swabs for COVID-19 and polymerase chain reaction (PCR) testing were positive in both cases (Table 1). In the first case, the patient complained of a skin rash, and further examination revealed a positive PCR test. In the second case, the COVID-19 symptoms and vasculitis developed simultaneously. In both cases, a skin biopsy confirmed the diagnosis of IgAV. In the second case, a kidney biopsy was performed, as IgAN developed. The authors hypothesized that COVID-19 causes IgA-mediated diseases with the deposition of immunoglobulin A in the skin and other organs and the development of vasculitis.

A similar case was described by Li et al[34]: a 30-year-old man with clinical signs of active COVID-19 infection presented with purpuric rash, joint, and abdominal pain, proteinuria, and hematuria. COVID-19 was verified by a positive throat swab and SARS-CoV-2 nucleic acid testing. The diagnosis of IgAV was confirmed by a biopsy of the skin and kidneys. A skin biopsy showed signs of leukocytoclastic vasculitis. Given the persistence of the urinary syndrome (proteinuria, hematuria), a kidney biopsy was performed, which showed signs of IgAN. Rowley and Shulman[35] found IgA plasma cell infiltration of the coronary arteries, pancreas, and kidneys in patients who died of Kawasaki disease. They hypothesized that the virus or pathogen invades through the respiratory or digestive tract, and IgA producing plasma cells affect the coronary arteries and heart muscles, etc. Comparative characteristics of the clinical cases are presented in Tables 1 and 2.

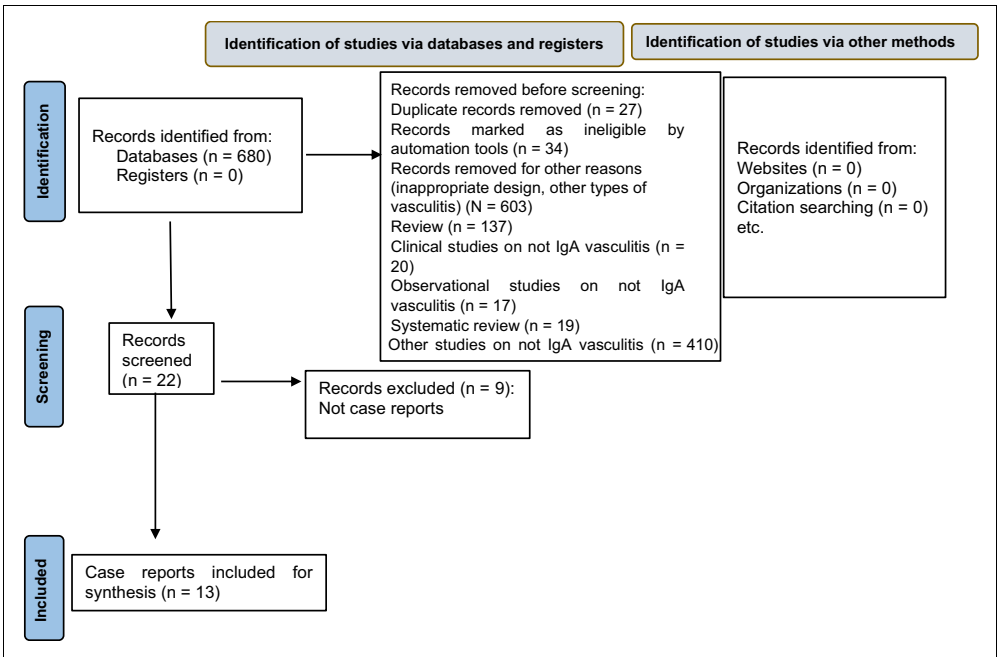

FIGURE 2
PRISMA diagram of search process.[52]

PEDIATRIC CASES

In children, IgAV most commonly affects males under 5 years of age. A 3-year-old male with palpable purpura and abdominal pain, without renal or musculoskeletal involvement, presented during an active COVID-19 infection.[36] A nasopharyngeal swab tested positive for SARS-CoV-2 using reverse transcriptase-PCR. He was diagnosed with IgAV after meeting 2 clinical criteria (palpable purpura and abdominal syndrome). AlGhoozi[37] also reported the case of a 4-year-old male with skin and joint symptoms 37 days after a COVID-19 upper respiratory infection. A PCR test performed 2 distinct times, 5 days apart, confirmed his COVID-19 positivity. The patient's clinical presentation was consistent with the EULAR/PRINTO/PRES criteria for IgAV,[21] as it met the requirement of a characteristic rash in the absence of thrombocytopenia, as well as one of the supportive criteria of acute arthralgia of the ankle joints. An additional case of a 2-year-old male positive for SARS-CoV-2 with gastrointestinal (hematochezia, vomiting streaked with blood, abdominal pain) and skin manifestation (palpable purpura and ecchymosis) without respiratory symptoms was recently published. Unlike other cases, the child had an elevated D-dimer (19.88 mg/ml) and c-reactive protein (2.5 mg/dl).[38] COVID-19 was diagnosed simultaneously with IgAV. COVID-19 was detected in a nasopharyngeal sample using PCR. A skin biopsy of the patient's right thigh revealed superficial perivascular inflammation with neutrophils and positive immunostaining for IgA.

A 16-year-old male developed a purpuric rash of his lower limbs and buttocks, severe abdominal pain, hematochezia, and hemoptysis 2 days before testing positive for SARS-CoV-2. This patient also had renal involvement, including severe proteinuria and hematuria. This patient was prescribed oral prednisoLONE for a month in combination with ramipril.[39] A similar case was described by Borocco et al[40] in a 13-year-old girl with a positive PCR for SARS-CoV-2 and Epstein-Barr virus. IgAV was diagnosed clinically according to EULAR/PRINTO/PRES criteria in both cases.

OLDER ADULT CASES

Five cases of IgAV in older adults were found in the literature. Suso et al[41] reported the case of a 78-year-old man with COVID-19 pneumonia, who developed cutaneous vasculitis, arthritis, and nephritic syndrome 5 weeks after COVID-19. The diagnosis of COVID-19 was made based

TABLE 1
Diagnostic findings of IgA vasculitis in patients with COVID-19

N	Reference	Age/sex	Diagnostic date/method for IgAV	Diagnostic date/method for COVID-19	The period from a positive PCR test to the appearance IgAV signs
1	Allez et al[32]	24 y/male	Not reported/skin biopsy H/E: perivascular and vessel wall infiltration by neutrophils and lymphocytes, leukocytoclasia DIF: C3 and IgA deposits in dermal capillaries	Not reported/ a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab. Positive serology for COVID-19.	Not reported
2	Suso et al[41]	78 y/male	3 wk after discharge date 17 April 2020/kidney biopsy H/E: segmental mesangial expansion with hypercellularity in 4/7 glomeruli, epithelial crescents in 2/7 glomeruli, without tubular or interstitial defects DIF: IgA granular deposits in the glomerular mesangium	4 April 2020/a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab. Positive result for anti-SARS-CoV-2 by chemiluminescent immunoassay.	5 wk
3	Sandhu et al[33]	22 y/male	Not reported/skin and kidney biopsy Skin biopsy: H/E: signs of LCV DIF: negative for IgA deposition (after 48 hours) Kidney biopsy H/E: signs of focal necrotizing, mesangial, and focal endocapillary proliferative IgA nephropathy DIF: IgA mesangial granular deposition	30 August 2020/a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab	Simultaneously
4	Jacobi et al[36]	3 y/male	Not reported/ clinically (palpable purpura and abdominal pain)	Not reported/ a positive RT-PCR of a nasopharyngeal swab.	Simultaneously
5	AlGhooziand AlKhayyat[37]	4 y/male	Not reported/ clinically (palpable purpura and arthralgia)	Not reported/a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab.	37 d

continued

TABLE 1
Continued

N	Reference	Age/sex	Diagnostic date/method for IgAV	Diagnostic date/method for COVID-19	The period from a positive PCR test to the appearance IgAV signs
6	Hoskins et al[38]	2 y/male	Not reported/ skin biopsy H/E: perivascular inflammation with neutrophils Immunostain: positive for IgA DIF: not performed	Not reported/ a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab.	Simultaneously
7	Li et al[34]	30 y/male	Not reported/skin and kidney biopsy Skin biopsy: H/E: a neutrophil-rich small-vessel vasculitis-LCV DIF: IgA, IgG, IgM, and C3 was negative Kidney biopsy: H/E: focally crescentic and segmentally necrotizing IgAN with focal endocapillary hypercellularity DIF mesangial and segmental peripheral capillary wall staining for IgA, C3, IgM, IgG, and C1q was negative E/M: mesangial and subendothelial immune-type deposits	Not reported/ a positive throat swab and nucleic acid testing for SARS-CoV-2.	Simultaneously
8	El Hasbani et al[39]	16 y/male	Not reported/ clinically (palpable purpura, abdominal pain, proteinuria, elevated Ig A)	Not reported/ a positive PCR test for SARS-CoV-2.	2 d

continued

TABLE 1
Continued

N	Reference	Age/sex	Diagnostic date/method for IgAV	Diagnostic date/method for COVID-19	The period from a positive PCR test to the appearance IgAV signs
9	Jedlowski and Jedlowski[30]	70 y/male	Not reported/skin and kidney biopsy Skin biopsy: H/E: signs of LCV DIF: IgA, C5B-9, fibrinogen deposition Kidney biopsy: H/E: mesangial hypercellularity, tubular atrophy, interstitial fibrosis, lymphocytic tubulitis with absence of crescents DIF: granular mesangial deposition of IgA. E/M: patchy effacement of podocytes	Not reported/ a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab.	Simultaneously (1 wk later after URI symptoms)
10	Borocco et al,[40]	13 y/female	April 2020/clinically (palpable purpura, arthralgia, periarticular edema, abdominal pain)	Not reported/ a positive RT-PCR of a nasopharyngeal swab.	Simultaneously
11	Barbetta et al[42]	62 y/male	Not reported/skin biopsy H/E: perivascular and interstitial lymphocytic infiltrate, with extravasated red blood cells, ectatic capillary vessels, endothelial cells with signs of swelling without atypia DIF: IgA deposition	Not reported/ a positive RT-PCR of a nasopharyngeal swab.	10 d

continued

TABLE 1
Continued

N	Reference	Age/sex	Diagnostic date/method for IgAV	Diagnostic date/method for COVID-19	The period from a positive PCR test to the appearance IgAV signs
12	Oñate et al[43]	84 y/male	Not reported/skin and kidney biopsy Skin biopsy: H/E: signs of LCV DIF: IgA, C5B-9, fibrinogen deposition Kidney biopsy: H/E: interstitial fibrosis, tubular atrophy, without crescents DIF: granular mesangial deposition of IgA. C3, IgM, IgG, C1q were negative	March 2020/ a positive PCR test for SARS-CoV-2 in a nasopharyngeal swab.	4 mo
13	Oñate et al I[43]	87 y/male	December 2020/skin biopsy H/E: signs of LCV DIF: perivascular granular IgA deposition	October 2020/ a positive serology for Ig G, negative for Ig M.	8 wk

DIF, direct immunofluorescence; EM, electron microscopy; H/E, hemoxylin-eosin; IgA, immunoglobulin A; IgAV, igA vasculitis; IgM, immunoglobulin M; 1gG, immunoglobulin G; C3, complement 3; C1q, complement 1q; c5B-9, complement 5B-9; LCV, leukocytoclastic vasculitis; RT-PCR, reverse transcriptase-polymerase chain reaction; URI, upper respiratory infection.

TABLE 2
Clinical and laboratorial characteristic of IgA vasculitis in COVID-19 patients

N	Reference/country	Age/sex	Concomitant diseases	Brief scenario	Treatment
1	Allez et al,[1] France	24 y/male	Crohn's disease	- COVID-19 symptoms: none - IgAV symptoms: skin rash, asymmetric arthralgia, periarticular swelling, and abdominal pain, palpable purpura on the legs and arms, swelling in the left hand, and pain in several joints on palpation. - Laboratory and instrumental findings: CRP, D-dimer, fibrinogen, and complement C4, IgA levels were all elevated. An enlarged ileitis on CT scan.	MethylPREDNISolone enoxaparin
2	Suso et al,[41] Spain	78 year/male	Hypertension, alcohol consumption, bladder cancer in remission	- COVID-19 symptoms: history of bilateral pneumonia with respiratory failure, treated with hydroxychloroquine, lopinavir/ritonavir, dexamethasone, ceftriaxone, azithromycin, and tocilizumab (IL-6). - IgAV symptoms: returned to the ER 3 wk later with wrist arthritis, lower limb purpura, and hypertension. - Laboratory findings: elevated creatinine, hypoalbuminemia, massive proteinuria (10 g/d), and hematuria with 60% dysmorphic red blood cells.	PrednisoLONE, methylPREDNISolone+ riTUXimab

continued

TABLE 2
Continued

N	Reference/country	Age/sex	Concomitant diseases	Brief scenario	Treatment
3	Sandhu et al,[33] India	22 y/male	No	- There was a simultaneous development of symptoms of COVID-19 and vasculitis: fever, abdominal pain, vomiting, and painful swelling of both ankle and wrist joints were the first symptoms of the illness accompanied by multiple purpura, edema of the joints 2 d later. - Laboratory findings: proteinuria, elevation of liver function test.	Dexamethasone, oral prednisoLONE, mycophenolate mofetil
4	Jacobi et al,[36] Israel	3 y/male	Hirschsprung disease	- COVID-19 symptoms: none - IgAV symptoms: a palpable purpuric rash on the buttocks and extensor surface of the lower extremities, abdominal pain and emesis. - Laboratory findings: microcytic anemia and mild thrombocytosis.	NSAIDs, predniSONE
5	AlGhoozi and AlKhayyat,[37] Bahrain	4 y/male	No	- COVID-19 symptoms: signs of upper respiratory tract infection. - IgAV symptoms: lower limb arthralgia and maculopapular rash, edema of the ankles. - Laboratory findings: normal full blood count, normal electrolytes, normal liver and renal function tests, normal coagulation profile, erythrocyte sedimentation rate and C reactive protein values.	Paracetamol

continued

TABLE 2
Continued

N	Reference/country	Age/sex	Concomitant diseases	Brief scenario	Treatment
6	Hoskins et al,[38] [d]Baltimore	2 y/male	No	- COVID-19 symptoms: none - IgAV symptoms: severe abdominal pain, purpuric rash, ecchymotic lesions, hematochezia, emesis was observed - Laboratory findings: elevated D-dimer. CRP and high inflammatory markers.	Steroids, low-molecular weight heparin
7	Li et al.[34] Canada	30 y/male	No	- There was a simultaneous development of symptoms of COVID-19 and vasculitis: fever, runny nose, cough, diarrhea, abdominal pain, painful purpuric rash to his lower extremities, distal upper extremities, and trunk. - Laboratory findings: proteinuria, mild hematuria, cholestatic liver enzymes elevated.	Steroids
8	El Hasbani et al,[39] United States	16 y/male	No	- COVID-19 symptoms: sore throat, muscle pain. - IgAV symptoms: palpable purpura both lower limbs, abdominal pain, hemoptysis, hematochezia. - Laboratory findings: elevated inflammatory markers (ESR,CRP) and serum Ig A, proteinuria, microscopic hematuria, hypogammaglobinemia, hypoalbuminemia.	PrednisoLONE, ramipril, trimethoprim/Sulfamethoxazole

continued

TABLE 2
Continued

N	Reference/country	Age/sex	Concomitant diseases	Brief scenario	Treatment
9	Jedlowski and Jedlowski,[30] United States	70 year/male	Dyslipidemia	- COVID-19 symptoms: rhinorrhea, shortness of breath, fever, chills. - IgAV symptoms: diarrhea, bilateral symmetrical arthralgia of wrists, ankles, and knees, abdominal pain, purpuric rash on the bilateral lower extremities and buttocks, hematochezia, enterocolitis, ileitis. - Laboratory findings: elevated inflammatory markers (ESR,CRP), proteinuria, gross hematuria, acute kidney injury (elevation of creatinine).	Dexamethasone, MethylPREDNISolone, predniSONE
10	Borocco et al,[40] French	13 y/female	Panhypopituitarism, suprasellar germinoma in remission	- COVID-19 symptoms: sore throat, pharyngitis. - IgAV symptoms: purpuric and ecchymosis lesion of lower limbs, buttocks. abdominal pain, arthralgia, periarticular edema. - Laboratory findings: leukocytosis with neutrophilia, lymphocytosis, elevation of CRP, Ig G and A.	Pain relievers

continued

TABLE 2
Continued

N	Reference/country	Age/sex	Concomitant diseases	Brief scenario	Treatment
11	Barbetta et al,[42] Italy	62 y/male	Diabetes mellitus, arterial hypertension	- COVID-19 symptoms: dyspnea, fever, bilateral interstitial pneumonia. - IgAV symptoms: purpuric rash of lower extremities, buttocks, abdominal pain, vomiting, hematochezia. - Laboratory findings: hematuria, proteinuria, glycosuria, hyaline cylinders.	CPAP, hydroxychloroquine, lopinavir/ritonavir, enoxaparin, MethylPREDNISolone 1 mg/kg
12	Oñate I[43] Spain	84 y/male	Arterial hypertension, dyslipidemia, atrioventricular block tricuspid endocarditis congestive liver disease, atrial flutter, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, axonal polyneuropathy	- COVID-19 symptoms: dyspnea, fever, bilateral interstitial pneumonia. - IgAV symptoms: palpable purpura, acute renal failure with increase creatinine, proteinuria - Laboratory findings: increase of creatinine, proteinuria, microhematuria, purpuric skin lesion, increase in IgA level,	Hydroxychloroquine, lopinavir/ritonavir, azithromycin, tocilizumab, anticoagulant drugs. MethylPREDNISolone, oral prednisoLONE, mycophenolate mofetil.
13	Oñate I[43] Spain	87 y/male	Hypertension, hypertensive cardiomyopathy, pulmonary hypertension, diverticulosis, prostate hyperplasia, cognitive impairment	- COVID-19 symptoms: upper respiratory tract infection, ipsilateral crackles. - IgAV symptoms: purpuric skin lesion in the lower limbs, increase in IgA levels. creatinine, proteinuria, microhematuria. - Laboratory findings: increase of creatinine, proteinuria, microhematuria, increase in Ig A level.	Amoxicillin-clavulanate, MethylPREDNISolone, oral prednisoLONE

IgA, immunoglobulin A; IgAV, IgA vasculitis; C4, component 4; CT, computed tomography; IL-6, interleukin 6; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; ER, emergency room; NSAIDS, non-steroidal anti-inflammatory drugs; CPAP, continuous positive airway pressure.

on a positive reverse transcription-PCR test for SARS-CoV-2 in a nasopharyngeal swab and a positive result for anti-SARS-CoV-2 by chemiluminescent immunoassay.

A 62-year-old patient with respiratory distress due to COVID-19 pneumonia developed cutaneous, renal, and gastrointestinal manifestations of IgAV 10 days after admission. The skin biopsy showed leukocytoclastic vasculitis and IgA deposits revealed on immunohistochemistry.[42] Similar cases of vasculitis with development of acute renal failure have been reported in patients 70, 84, and 87 years old (Tables 1 and 2).[30,43]

It should be noted that in all cases, older adults had kidney damage, and 4 of them developed acute renal failure. Thus, more severe forms with renal involvement were observed in the older adult patients.

The Link Between COVID-19 and Vasculitis

It is known that IgA levels increase in inflammatory diseases such as AIDS, IgAN, IgAV, dermatitis herpetiformis, celiac disease, inflammatory bowel disease, Sjögren's syndrome, ankylosing spondylitis, and alcoholic liver cirrhosis. It is unclear what role IgA plays in these inflammatory disorders.[44] We believe that it is critical to be aware of the potential link between COVID-19 infection and IgA vasculitis. One of the possible mechanisms of microvascular injury and thrombosis is the deposition of C5b-9, C4d complement complexes, and co-localization of COVID-19 spike glycoproteins in endothelial cells, which activate pathways of the complement system. The activation of the complement system leads to the activation of the clotting pathway and fibrin deposition with thrombus formation.[45] The main causes of death due to COVID-19 are hypercoagulability, vasculitis, cytokine storm with the development of ARDS, and multiorgan failure syndrome.[46] A recent study of Zhang et al[47] showed that treatment with anti-inflammatory medications (glucocorticoids, IL-6 antagonist, JAK inhibitors, and chloroquine/hydroxychloroquine) can prevent severe complications and mortality due to COVID-19.

BIOLOGICAL PLAUSIBILITY

SARS-COV-2, the etiological agent of coronavirus infection, is known to cause vasculitis-like diseases. Clinical data also show a higher prevalence of Kawasaki disease (KD) in pediatric patients with COVID-19.[48] The pathophysiology of KD is based on extensive endothelial dysfunction. Some scientists suggest that KD vasculitis is a type of IgA vasculitis that involves the gut-vascular system.[49] COVID-19 affects skin cells, endothelial cells across the whole body via angiotensin-converting enzyme 2, thus leading to generalized endothelial damage and inflammation, so-called endotheliitis. SARS-COV-2 virus penetrates human cells by binding to angiotensin-converting enzyme transmembrane protein receptors of vascular endothelium and can cause systemic inflammatory response with subsequent development of a cytokine storm, which may play a role in the development of IgAV.[36] In addition, medications used to treat SARS-COV-2 (ie, antibiotics, TNF-alpha blockers, immunomodulatory agents) can cause drug-induced IgAV, which can also be one of the possible mechanisms of the development of vasculitis.[50] In 7 of our reviewed cases, SARS-CoV-2 infection preceded the development of IgA vasculitis. The latency time between infection and the onset of vasculitis ranged from 2 days to 4 months. These data support the theory of immune dysregulation as the main etiopathogenic factor of IgAV. In 6 cases, there were simultaneous manifestations of symptoms of COVID-19 and IgA vasculitis. In these cases with simultaneous manifestations, we considered the simultaneous presentation may have been due to delayed COVID-19 diagnosis, delayed health care utilization, or an asymptomatic course of SARS-CoV-2 infection.

Limitations

We have some limitations in our study. The small number of clinical cases makes it challenging to draw any definitive conclusions or establish a causal relationship between COVID-19 and IgAV. The absence of exact dates and methods of the diagnosis of COVID-19 infection and IgAV in the included case reports is a notable limitation as well. Finally, published case reports may reflect clinician and publication bias. The claim that IgAV affects men is premature. There is clear and abundant literature that chronic inflammatory and autoimmune processes are more prevalent in women[51] and that women experience substantially longer diagnostic delays and have symptoms and presentations that are often dismissed, misdiagnosed, considered vague, or not taken as seriously by health care providers and scientists. A fair and balanced interpretation must include that the published reports may reflect clinician and publication bias that tend to be much more (and unjustly) sensitive and responsive to men in the health care system, science, and publishing rather than a true underlying sex difference in prevalence and pathology.

Conclusion

COVID-19 associated IgAV affects mostly adults; it is characterized by a more severe course of the disease due to renal involvement. As the number of patients with COVID-19 increases worldwide, we suspect to see more cases of IgA-related disorders, especially IgAV, and it may indicate a severe course of infection. In asymptomatic patients with SARS-CoV-2, emergency care providers should maintain an index of suspicion for vascular damage. Emergency clinicians who note the possibility of IgAV in their differential diagnosis for patients with COVID-19 infection should consider referral to hematologist and recommend the following diagnostic testing: skin and kidney biopsy with direct immunofluorescence. Anticoagulants, glucocorticoids, and intravenous immunoglobulin are used to treat COVID-19–associated IgAV.[30,31] Further studies are warranted to determine the role of SARS-CoV-2 in the pathogenesis of IgAV and further clarify these relationships. It is important for emergency clinicians to be aware of the prevalence and presentation of COVID-19–mediated IgAV to assist in timely recognition and treatment of the condition.

Data, Code, and Research Materials Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Disclosures

Conflicts of interest: none to report.

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