INTRODUCTION

Immunoglobulin A (IgA) vasculitis or Henoch–Schönlein purpura (HSP) is a well-described autoimmune condition classically occurring alongside or shortly after an upper respiratory infectious (URI) trigger.1 IgA vasculitis in adults is rare, representing only 10% of cases with triggers including medications and less commonly malignancy.1,2 Recently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with resultant coronavirus disease 2019 (COVID-19) has been linked to vasculitides, such as multisystem inflammatory disease of children predominantly in pediatric patients and urticarial vasculitis in middle-aged to elderly adults. However, the role of COVID-19 in precipitating IgA vasculitis is unconfirmed. Here, we report a case of COVID-19-associated IgA vasculitis in an adult patient with significant renal involvement and perform a literature review to collate all reported cases of suspected COVID-19-associated IgA vasculitis.

CASE REPORT

A 70-year-old man developed URI symptoms including rhinorrhea, shortness of breath, fever, and chills after attending a gathering with known COVID-positive contacts. One week later, he developed
diarrhea and bilateral symmetrical arthralgias of the wrists, ankles, and knees, and presented with abdominal pain, diarrhea, and a purpuric rash on the bilateral lower extremities, buttocks, and abdomen. An intranasal swab for SARS-CoV-2 antigen was positive on admission; he had not received COVID-19 vaccination. Physical examination revealed palpable petechiae on the bilateral dorsal feet and pedal arches with extension proximally onto the bilateral thighs and abdomen, where purpuric plaques were noted (Figure 1).

Laboratory investigations were notable for elevated erythrocyte sedimentation rate and C-reactive protein to 40 mm/h (reference range, 0–20) and 7.71 mg/dL (reference range, 0–8), respectively. The patient’s urine protein/creatinine ratio was 4479 mg/g (reference range, 0–30 mg/g creatinine) and urinalysis was notable for 28 red blood cells (RBC)/high-power field (HPF) (reference range, 0–3). He was prescribed 6 mg oral dexamethasone for 8 days and thereafter lost to follow-up for 1 month and returned with hematochezia and acute kidney injury, evidenced by worsening of serum creatinine from baseline of 0.8 mg/dL (reference range, 0.7–1.4) to 3.8 mg/dL. Urinalysis revealed gross hematuria with 315 RBC/HPF and urine protein/creatinine ratio of 1790 mg/g creatinine.

Punch biopsy of a purpuric plaque on the abdomen with hematoxylin–eosin (HE) was notable for leukocytoclastic vasculitis (LCV). Direct immunofluorescence (DIF) was notable for strong signal granular IgA deposition and weaker signal C3, C5B-9, and fibrinogen deposition surrounding the vasculature of the superficial papillary dermis. A kidney biopsy HE demonstrated mesangial hypercellularity, focal/mild endocapillary hypercellularity, tubular atrophy, interstitial fibrosis, and lymphocytic tubulitis, without crescents. DIF showed granular mesangial deposition of IgA (2+), with identification of patchy effacement of podocytes on electron microscopy. He was diagnosed with IgA vasculitis, and he was prescribed methylprednisolone 500 mg i.v. for 3 days followed by prednisone 1 mg/kg p.o. At 1-month follow-up, the patient had significant improvement of creatinine to 2.1 mg/dL, improvement in urine protein/creatinine ratio to 505.6 mg/g, and resolution of abdominal pain and rash. The patient provided written informed consent to publication of his case details.

A literature review was performed which identified nine cases of IgA vasculitis associated with a diagnosis of COVID-19, in addition to our case (Table 1). Three of these cases lacked biopsy data and another reported LCV on skin biopsy but lacked positive confirmatory IgA screening with immunostaining or DIF. However, these cases met European League Against Rheumatism, Pediatric Rheumatology International Trials Organization, and Pediatric Rheumatology European Society criteria for HSP and were included. All reported cases of COVID-19-associated IgA vasculitis were in males, as opposed to the slight male sex predilection (56–57%) seen in other IgA vasculitis cases reported previously (χ²-test, p = 0.005). Pediatric patients represented five of 10 (50%) cases with patients aged 4 years or less comprising three of these. The remainder occurred in adult patients (5/10, 50%). Compared to previously reported cases of IgA vasculitis in which 90% occurred in pediatric populations, COVID-19-associated IgA vasculitis more commonly occurred in adults (50% of cases) (χ²-test, p < 0.00002). Time from COVID-19 symptom onset to development of IgA vasculitis ranged 2–37 days. While all patients were noted to be COVID-19-positive prior to vasculitis onset, five of the 10 (50%) patients were positive for SARS-CoV-2 at presentation. Kidney and skin biopsy results were available in four and six of the 10 cases, respectively. All skin biopsy results were notable for LCV on HE, with DIF positive for IgA in 40% of cases (2/5) in which DIF was performed. All kidney biopsies were positive for IgA on DIF and electron microscopy results varied from mesangial and/or subendothelial deposits to podocyte effacement.

![Figure 1](image-url) (a) Palpable petechiae on the arch and dorsal foot. (b) Extension of palpable purpuric plaques onto the bilateral thighs. (c) Purpuric papules on the abdomen
| Study            | Patient age, gender | PMHx                                      | COVID on admission, time after COVID to symptom onset (if specified) | Clinical manifestations | Organ systems involved / Biopsy findings | Treatment / Follow up                  |
|------------------|---------------------|-------------------------------------------|---------------------------------------------------------------------|-------------------------|-----------------------------------------|----------------------------------------|
| Suso et al 2020  | 78, Male            | Alcohol use disorder HTN Dyslipidemia Bladder cancer (s/p transurethral resection) | Negative Time to symptom onset: 3 weeks                           | Palpable purpura:       | Kidney: (Massive proteinuria (>10 g/day, hematuria, acute kidney injury [Cr from baseline 0.78 mg/dl → 1.96 mg/dl]), skin, joints | Prednisone 40 mg Qday – > IV pulse methylprednisolone + rituximab Discharged on PO prednisone Follow up: Not available |
|                  |                     |                                           |                                                                     |                         | Organ systems:                          |                                        |
|                  |                     |                                           |                                                                     |                         | Kidney:                                  |                                        |
|                  |                     |                                           |                                                                     |                         | • H&E: Mesangial expansion with hypercellularity, crescents in 2/7 glomeruli, no tubules or interstitial defect |                                        |
|                  |                     |                                           |                                                                     |                         | • DIF: granular IgA in mesangium on DIF |                                        |
|                  |                     |                                           |                                                                     |                         | • EM: Mesangial deposits and podocyte effacement |                                        |
|                  |                     |                                           |                                                                     |                         |                                        |                                        |
| Allez 2020       | 24, Male            | Crohns on adalimumab                      | Positive (negative day after admission)                           | Palpable purpura:       | GI tract (ileitis and bowel wall thickening on CT), skin, joints, elevated inflammatory markers, d-dimer and serum IgA | Enoxaparin, IV methylprednisolone 0.8 mg/kg Discharged on 7 days PO steroids and enoxaparin Follow up: Not available |
|                  |                     |                                           |                                                                     |                         | Organ systems:                          |                                        |
|                  |                     |                                           |                                                                     |                         | Kidney:                                  |                                        |
|                  |                     |                                           |                                                                     |                         | • H&E: Perivascular and vessel wall infiltration by PMNs and lymphocytes, leukocytoclasia, LCV |                                        |
|                  |                     |                                           |                                                                     |                         | • DIF: C3/IgA deposits on dermal capillaries |                                        |
|                  |                     |                                           |                                                                     |                         |                                        |                                        |
| Hoskins 2021     | 2, Male             | –                                        | Positive                                                             | Palpable purpura:       | GI tract (EDG with erythema, superficial stomach erosion), elevated inflammatory markers and d-dimer | Enoxaparin, IV steroids (unspecified) Discharged on PO steroid (unspecified) with 4-week taper, ASA 81 mg, PPI Follow up: at 1 week: Resolution of symptoms |
|                  |                     |                                           |                                                                     |                         | Organ systems:                          |                                        |
|                  |                     |                                           |                                                                     |                         | Kidney:                                  |                                        |
|                  |                     |                                           |                                                                     |                         | • H&E: Superficial perivascular inflammation with neutrophils, LCV |                                        |
|                  |                     |                                           |                                                                     |                         | • Immunostain: IgA positive               |                                        |
|                  |                     |                                           |                                                                     |                         | • DIF: not performed                     |                                        |
|                  |                     |                                           |                                                                     |                         | Stomach:                                 |                                        |
|                  |                     |                                           |                                                                     |                         | • Gastritis w/o capillaritis              |                                        |
|                  |                     |                                           |                                                                     |                         |                                        |                                        |
| Jacobi 2020      | 3, Male             | Surgical corrected Hirschprung            | Positive                                                             | Palpable purpura:       | GI tract (abdominal US with increased bowel wall thickness), skin, joints | NSAIDs, readmitted on methylprednisolone 2 mg/kg × 3 days Follow up: Not available |
|                  |                     |                                           |                                                                     |                         | Organ systems:                          |                                        |
|                  |                     |                                           |                                                                     |                         | Kidney:                                  |                                        |
|                  |                     |                                           |                                                                     |                         | • H&E: Mesangial expansion with hypercellularity, crescents in 2/7 glomeruli, no tubules or interstitial defect |                                        |
|                  |                     |                                           |                                                                     |                         | • DIF: granular IgA in mesangium on DIF |                                        |
|                  |                     |                                           |                                                                     |                         | • EM: Mesangial deposits and podocyte effacement |                                        |

(Continues)
| Study       | Patient age, gender | PMHx | Clinical manifestations | Organ systems involved / Biopsy findings | Treatment/Follow up |
|------------|---------------------|------|-------------------------|----------------------------------------|---------------------|
| **Li 2021** | 30, Male            |      | Palpable purpura:       | Organ systems:                          | Treatment:          |
|            |                     |      | • Lower extremities,    | Kidney (UA with proteinuria, microscopic hematuria, creatinine unaffected), GI tract (ALP/GGT elevation), skin, wrists, inflammatory marker and D-dimer elevation | Prednisone 40 mg x 7 days, losartan 25 mg daily |
|            |                     |      | distal upper            |                                        | Follow up at 6 weeks:  |
|            |                     |      | extremities, trunk      |                                        | Preserved renal function, reduced proteinuria (protein cr/ratio = 128.6 mg/mmol), UA with ongoing hematuria 30 RBC/HPF |
|            |                     |      | Bilateral wrist arthritis | Biopsy findings:                        |                      |
|            |                     |      | Fever                   | Skin:                                  |                      |
|            |                     |      | Diarrhea                | • H&E: Neutrophil-rich small vessel vasculitis, LCV |                      |
|            |                     |      | Abdominal pain          | • IF: negative for IgA, IgG, IgM and C3 |                      |
|            |                     |      | Frothy urine w/o gross hematuria | Kidney biopsy: |                      |
|            |                     |      |                         | • H&E: 5% global sclerosis and 5% segmental sclerosis, tubular atrophy and interstitial fibrosis, |                      |
|            |                     |      |                         | • DIF: Mesangial and segmental capillary staining |                      |
|            |                     |      |                         | 3+ IgA, C3 2+, trace IgM and IgG, C1q negative |                      |
|            |                     |      |                         | • EM: Mesangial and subendothelial immune deposits |                      |
|            |                     |      |                         |                                        |                      |
| **Sandhu 2021** | 22, Male           |      | Palpable purpura:       | Organ systems:                          | Treatment:          |
|            |                     |      | • Upper extremities,    | Kidney (proteinuria 2 g/day), GI (LFT mild elevation), skin, joints | Dexamethasone 0.1 mg/kg IV for 10 days. |
|            |                     |      | lower extremities       | Biopsy findings:                        |                      |
|            |                     |      | Bilateral arthralgias of ankles, wrists | Skin: |                      |
|            |                     |      | Fever                   | • H&E: plump endothelial cells, perivascular mixed inflammatory infiltrate with PMNs and lymphocytes, extravasation of RBCs, capillaries with fibrinoid change of vessel wall, LCV |                      |
|            |                     |      | Abdominal pain          | • IF negative (false?) |                      |
|            |                     |      | Non-bilious emesis      | Kidney: |                      |
|            |                     |      |                         | • H&E: Mesangial and endocapillary proliferation, crescents |                      |
|            |                     |      |                         | • DIF: Mesangial granular IgA cellular crescent formation |                      |
| **AlGhoozi 2021** | 4, Male            |      | Palpable purpura:       | Organ systems:                          | Treatment:          |
|            |                     |      | • Lower extremities,    | Skin, joints                           | APAP PRN           |
|            |                     |      | buttocks                | Biopsy findings:                        |                      |
|            |                     |      | Bilateral arthralgias of ankles | No biopsies performed |                      |
|            |                     |      | Edema bilateral ankles  |                                        |                      |
|            |                     |      |                         |                                        |                      |

**TABLE 1** (Continued)
### TABLE 1

| Study          | Patient age, gender | PMHx | COVID on admission, time after COVID to symptom onset (if specified) | Clinical manifestations | Organ systems involved / Biopsy findings                                                                 | Treatment/Follow up |
|----------------|---------------------|------|---------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------------------|---------------------|
| Kumarr 2021    | 13, Male            | –    | Not performed at admission, positive 4 weeks prior Time to symptom onset: 4 weeks | Palpable purpura: • Lower extremities, buttocks Hematuria | Organ systems: Kidney (hematuria), skin Biopsy findings: Skin: • H&E: Epidermal necrosis with intraepidermal pustules, small vessel neutrophilic LCV • DIF: Negative for IgA | Treatment: Prednisolone 1 mg/kg PO for 2 weeks followed by taper over 4 weeks Follow up at 4 weeks: Improved but persistent lesions at 4 weeks on prednisone taper |
| El Hasba 2021  | 15, Male            | –    | Yes, also positive 14 days prior Time to symptom onset: 2 days        | Palpable purpura: • Lower extremities, buttocks Abdominal pain Hemoptysis Hematochezia | Organ systems: Kidney (proteinuria, microscopic hematuria), GI tract (hemoptysis, hematochezia), skin Biopsy findings: No biopsies performed | Treatment: Prednisolone 30 mg daily, ramipril 2.5 mg daily, trimethoprim/sulfamethoxazole prophylaxis Follow up at 2 and 6 weeks: • Two weeks: Less proteinuria (3651 mg/24 h → 2870 mg/24 h) • Six weeks: Resolution of rash, proteinuria to 780 mg/24 h |
| Jedlowski 2021 | 70, Male            | Dyslipidemia | Positive (negative at re-presentation) Time to symptom onset: 1 week | Palpable purpura: • Lower extremities, buttocks, abdomen Abdominal pain Enterocolitis Ileitis Hematochezia Gross hematuria | Organ systems: Kidney (proteinuria, gross hematuria, acute kidney injury [Cr from baseline 0.8 mg/dl → 3.8 mg/dl]), GI tract (ileitis, enterocolitis), skin, joints Biopsy findings: Skin: • H&E: Perivascular mixed inflammatory infiltrate with PMNs and lymphocytes, leukocytoclasia, LCV • DIF: granular IgA deposits and weaker signal C3, C5B-9 and fibrinogen deposition surrounding the superficial papillary dermis vasculature Kidney: • H&E: mesangial hypercellularity, focal/mild endocapillary hypercellularity, tubular atrophy, interstitial fibrosis and lymphocytic tubulitis but without crescent • DIF: granular mesangial deposition of IgA (2+) • EM: patchy effacement of podocytes | Treatment: Dexamethasone 6 mg PO × 8 days, methylprednisolone 500 mg IV ×3 days, prednisone 1 mg/kg PO ×1 month Follow up (interval and 1 month): Symptoms resolved with dexamethasone initially, then with methylprednisolone. At 1 month follow up, improvement in creatine and urinary protein |

**Abbreviations:** ALP, alkaline phosphatase; APAP, acetaminophen; ASA, aspirin; COVID-19, coronavirus disease 2019; Cr, creatinine; CT, computed tomography; DIF, direct immunofluorescence; EGD, esophagogastroduodenoscopy; EM, electron microscopy; GGT, gamma-glutamyl transferase; GI, gastrointestinal; HE, hematoxylin–eosin; HPF, high-power field; HTN, hypertension; i.v., intravenous; IV, intravenous; LCV, leukocytoclastic vasculitis; LFT, liver function test; NSAID, non-steroidal anti-inflammatory drug; p.o., oral; PMN, polymorphonuclear cells/neutrophils; PPI, proton pump inhibitor; PRN, as needed; RBC, red blood cells; s/p, status post; UA, urinalysis; US, ultrasound.
Organs involved included the skin, joints, gastrointestinal tract, and renal systems. Acute kidney injury and proteinuria occurred exclusively in adult patients. However, when adult and pediatric cases were compared for differences in clinical presentation, arthralgias reached statistical significance ($p = 0.04$) while proteinuria approached statistical significance ($p = 0.07$) (Table 2). There was no difference in organ system involvement between adult and pediatric patients. Nine of 10 cases were treated with corticosteroids. In the 10th case the patient was treated with acetaminophen. Follow-up information was available in seven cases; six cases received corticosteroids with improvement. The case treated with acetaminophen had persistence of rash and microscopic hematuria.

3 | DISCUSSION

Immunoglobulin A vasculitis is a systemic, non-granulomatous, multiorgan, immune complex-mediated LCV that often occurs after a URI with an associated dysregulated IgA-mediated immune response to bacterial or viral antigens. This small vessel vasculitis is defined clinically by the presence of gastrointestinal symptoms, polyarthralgias, renal dysfunction, and non-thrombocytopenic palpable purpura.

Historically, IgA vasculitis has been predominantly a pediatric condition with rare adult cases. The annual incidence is approximately 15/100 000 in children and 1.3/100 000 in adults. Kang et al. performed a retrospective study comparing the laboratory data, clinical features, and outcomes in pediatric versus adult patients with IgA vasculitis. This study found an association between sex and development of IgA vasculitis, with most adult and pediatric cases occurring in males (56.2% in adults, 57.1% in children). There was no statistically significant difference with regards to prior URI (22.9% in adults, 36.6% in children), but malignancy (10.4%) and former drug exposure (12.5%) were identified as precipitating factors only in adults. Renal outcomes were worse in adults who frequently experienced persistent proteinuria/hematuria (58.3% vs. 29.5%) with higher rates of chronic renal failure development (10.4% vs. 1.8%).

In our study, a comparison between adult and pediatric cases was similarly performed. Unlike classical cases of IgA vasculitis, cases related to COVID-19 were more common in adults (50.0% of cases). However, it should be noted that most COVID-19 cases occur in adults, which may contribute to this discrepancy. There was no significant difference between the two groups with regards to organ involvement overall except for arthralgias, which were more common in adults ($p = 0.04$), and proteinuria, which trended towards significance ($p = 0.07$). Of note, within the present study all patients were male and more patients were adults, which is a statistically significant difference between COVID-19-associated and classical IgA vasculitis.

| All cases (n = 10) | Adult cases (n = 5) | Pediatric cases (n = 5) | $p$ (adult vs. child) |
|------------------|-------------------|------------------------|----------------------|
| Average age (years) | 26.2 | 44.8 | 7.6 | 1.00 |
| COVID + on admission | 6 (60.0) | 3 (60.0) | 3 (60.0) | 1.00 |
| Skin and joint Involvement | | | | |
| Skin overall | 10 (100.0) | 5 (100.0) | 5 (100.0) | 1.00 |
| Lower extremity | 9 (90.0) | 5 (100.0) | 4 (80.0) | 0.35 |
| Upper | 5 (55.6) | 3 (60.0) | 2 (40.0) | 0.58 |
| Buttocks/Trunk | 6 (55.6) | 2 (40.0) | 4 (80.0) | 0.24 |
| Joints/arthralgias | 7 (77.8) | 5 (100.0) | 2 (40.0) | 0.04 |
| GI Involvement | | | | |
| GI overall | 7 (70.0) | 4 (80.0) | 3 (60.0) | 0.54 |
| Abdominal pain | 7 (70.0) | 4 (80.0) | 3 (60.0) | 0.54 |
| Nausea/vomiting | 4 (40.0) | 1 (20.0) | 3 (60.0) | 0.24 |
| Diarrhea | 2 (20.0) | 2 (40.0) | 0 (0.0) | 0.14 |
| Hematochezia | 2 (20.0) | 1 (20.0) | 1 (20.0) | 1.00 |
| Renal involvement | | | | |
| Renal overall | 6 (60.0) | 4 (80.0) | 2 (40.0) | 0.24 |
| Microscopic hematuria | 3 (30.0) | 1 (20.0) | 2 (40.0) | 0.54 |
| Gross hematuria | 2 (20.0) | 2 (40.0) | 0 (0.0) | 0.14 |
| Proteinuria | 5 (40.0) | 4 (80.0) | 1 (20.0) | 0.07 |
| Acute kidney injury | 2 (20.0) | 2 (40.0) | 0 (0.0) | 0.14 |
The pathogenesis of COVID-19-associated IgA vasculitis may be related to faulty development of a type 2 T-helper (Th2) response to the virus and development of IgA vasculitis. Patients with more severe cases of COVID-19 inappropriately mount a Th2 response, resulting in the activation of B cells and production of antibodies. Presumably, given the high antigen load, a type 3 hypersensitivity reaction occurs with accumulation of antigen–antibody complexes. Resultant deposition of antigen–antibody complexes, most commonly in blood vessels, occurs with subsequent activation of the complement cascade and release of complement anaphylatoxins (C3a and C5a), ultimately resulting in LCV. Interestingly, recent reports also suggest development of new-onset or reactivation of IgA vasculitis in response to COVID-19 vaccination. These observations strengthen the likelihood of an antigen–antibody complex-mediated process, possibly due to the SARS-CoV-2 spike protein, underlying the development of COVID-19-associated IgA vasculitis.

ACKNOWLEDGMENTS
None.

CONFLICT OF INTEREST
None declared.

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How to cite this article: Jedlowski PM, Jedlowski MF. Coronavirus disease 2019-associated immunoglobulin A vasculitis/Henoch–Schönlein purpura: A case report and review. J Dermatol. 2022;49:190–196. https://doi.org/10.1111/1346-8138.16211