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Case Series

A Case Series of Unusual IgA Vasculitis

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Abstract

Introduction
Immunoglobulin A vasculitis (IgA)is a rare condition characterized by palpable purpura, often involving the skin, gastrointestinal tract, joints, and kidneys. Presentation is usually acute and is more common in children and adolescents of Southeast Asian and European descent. In the adult population, it is less common and therapies are not as well-established.

Case Presentation
Disease prevalence of IgA vasculitis outside Southeast Asian and European populations is not well-documented. In this case series, we present 2 cases of IgA vasculitis in 2 older adult males, one of Native American descent and one of African American descent.

Conclusion
IgA vasculitis must be considered within the adult population, and it is not limited to certain ethnic groups. Further research is needed to give clarity on the best treatment options for adults with IgA vasculitis. We believe that patients presenting with IgA vasculitis are best managed in a multidisciplinary approach, especially those patients with limited improvement despite the initiation of corticosteroids. Our 2 cases should raise awareness of IgA vasculitis in patients with skin rashes and elevated creatinine levels.

Keywords
adult; Henoch-Schönlein purpura (HSP); IgA vasculitis

Introduction
Immunoglobulin A (IgA) vasculitis, formally Henoch-Schönlein Purpura, is a small vessel vasculitis with IgA1-dominant immune complex deposits, affecting small vessels. IgA vasculitis most commonly affects children and adolescents, with a reported annual incidence rate of 3-26.7/100 000, though this number is likely underestimated.[1,2] Adults are less commonly affected, with an annual incidence rate of 0.8-1.8/100 000.[1] Both adolescent and adult males have a reported higher incidence of IgA vasculitis when compared to females. IgA vasculitis is most prevalent in Southeast Asia and to a lesser extent in Europe and North America, but it is rare in Africa.[1,3] Multiple sets of criteria have been used for the diagnosis of IgA vasculitis. The European League Against Rheumatism, the Pediatric Rheumatology International Trials Organization, and the Pediatric Rheumatology European Society have proposed a validated classification criterion with high sensitivity and specificity that includes the presence of purpura or petechiae (mandatory) with lower limb predominance plus 1 of the following criteria: abdominal pain, histopathology positive for IgA, arthritis or arthralgia, or renal involvement.[4] This article presents 2 cases of IgA vasculitis in 2 older adult males—a Native American and an African American.

Case Presentation
Case 1
A 56-year-old Native American male with a past medical history of diabetes mellitus-type 2 (DMII), hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetic neu-

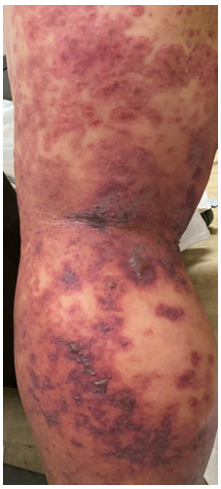

Figure 1. A posterior view of the left lower extremity demonstrated palpable purpura.

ropathy, and hypothyroidism presented to the emergency department (ED) for evaluation of a rash and swelling in both hands and feet. For 2 days prior to presentation, the patient noted a painless, nonpruritic, palpable purpura and petechiae on the hands and arms that spread to the abdomen, flank, and legs on the day of presentation (**Figures 1 and 2**). The patient stated that the rash started on the dorsum of his hands and spread to the upper arms, lower abdomen, back, and lower extremities but did not involve the palms, soles, or face. Lesions developed 24 hours after eating shrimp fried rice and chicken. Additionally, he and several family members developed diarrhea, lower abdominal cramping, and nausea. A laboratory evaluation revealed a creatinine of 1.5 mg/dL and an estimated glomerular filtration rate via Cockcroft-Gault equation of 54 mL/min. A urinalysis demonstrated 2+ blood, 0-2 red blood cell count (RBC)/high-powered field, 100 mg/dL protein, and rare mucus. Otherwise, the laboratory studies were noncontributory initially. Initial labs are listed in **Table 1**. Further laboratory studies, including an antineutrophilic cytoplasmic antibody (ANCA) test, an antinuclear antibody (ANA) test, and a syphilis screen were obtained. At that time, the patient was discharged from the ED with close dermatology follow-up.

The patient presented to the ED again 8 days later for evaluation of dizziness, vomiting, abdominal pain, development of arthritic pain in the fingers and knees, and no improvement of palpable purpura. The patient was initially hypotensive and responded to a fluid bolus and antiemetics. Laboratory studies were found to not have significantly changed since his previous visit. The ANA screen was negative; the cytoplasmic-ANCA was less than 1:20; the perinuclear-ANCA was less than 1:20; and the

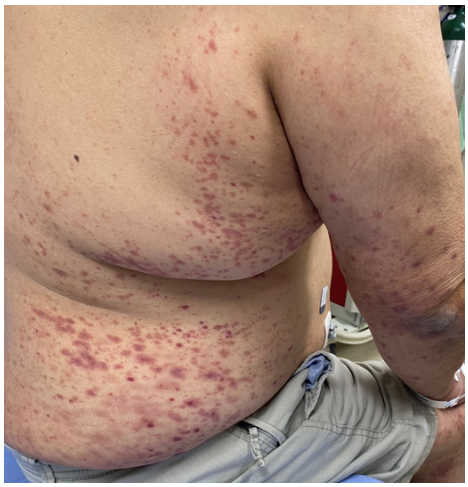

Figure 2. The right flank showed involvement of palpable purpura.

Table 1. Initial Laboratory Values of Case #1

Test	Result	Reference range
White blood cell count	16.6 x 10^9/L	4-10.9 x 10^9/L
Hemoglobin	15.4 g/dL	13.5-16.5 g/dL
Platelet count	316 x 10^9/L	135-350 x 10^9/L
Sodium	122 mEq/L	136-145 mEq/L
Chloride	81 mEq/L	101-111 mEq/L
Glucose	273 mg/dL	70-100 mg/dL
Creatinine	1.2 mg/dL	0.7-1.2 mg/dL
BUN	33 mg/dL	6-20 mg/dL
Albumin	2.8 g/dL	3.4-4.8 g/dL
ESR	66 mm/hr	0-20 mm/hr
C3	89 mg/dL	82-167 mg/dL
C4	17 mg/dL	12-38 mg/dL
IgA	249 mg/dL	61-437 mg/dL
Anti-streptococcal antibody	134 units/mL	0-120 units/mL
Urine blood	2+	Negative
Urine RBC	0-2/high power field	0-2/high power field
Urine protein	100 mg/dL	Negative mg/dL

Abbreviations: BUN = Blood, urea, nitrogen; ESR = erythrocyte sedimentation rate; RBC = red blood cell

rapid plasma reagin test was non-reactive. The computed tomography angiography scan of the abdomen and pelvis demonstrated normal appearing large vessels without evidence of vasculitis, but the scan did show an abnormal appearance at the distal small bowel with mucosal thickening and edema with inflammatory changes involving the cecum. The skin punch biopsy revealed leukocytoclastic vasculitis. The patient eventually underwent a renal biopsy, and it was consistent with IgA nephropathy (**Figure 3**).

Several days into the hospital course, the patient continued to have diarrhea. On average, he had 3-4 liquid bowel movements daily along with some streaking of blood. A capsule endoscopy revealed duodenal, jejunal, and ileal erosions as well as ulcers and a submucosal hemorrhage consistent with vasculitis. An

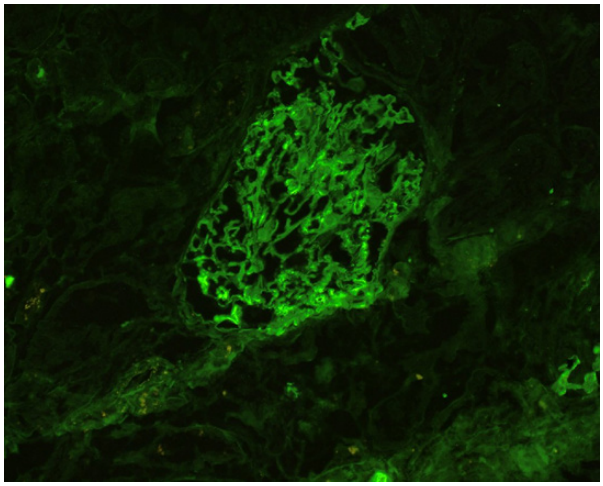

Figure 3. Immunofluorescence staining of glomeruli demonstrated granular, mesangial staining for IgA. Courtesy of Arkana Laboratories.

esophagogastroduodenoscopy demonstrated esophagitis. However, examined portions of the small bowel were nonrevealing. The patient declined a colonoscopy evaluation. Given the evidence of small intestine involvement, the patient was started on glucocorticoids.

On hospital day 11, the patient noted improvement in diarrhea and joint pain. Renal function remained stable, and we determined the patient was stable enough for discharge. The patient was prescribed a prednisone taper of 60 mg daily for the first 7 days, then 40 mg daily for 7 days, and finally 20 mg daily for 7 days. He was also prescribed proton pump inhibitor therapy given his esophagitis and a protracted course of steroids. We recommended he follow-up with rheumatology for close monitoring of his IgA vasculitis and gastroenterology for a colonoscopy. Renal function remained stable 16 months after discharge, with a creatinine of 1.2 mg/dL and an estimated glomerular filtration rate via Cockcroft-Gault equation of 67 mL/min.

Case 2

A 69-year-old African American male with a past medical history of bilateral lower extremity venous insufficiency, congestive heart failure, chronic kidney disease stage IIIB, and DMII presented to the ED with complaints of bilateral leg wounds. His leg wounds were chronic in nature and had recently started oozing. The wounds were causing him considerable discomfort, prompting him to seek care with his primary care physician. As there was concern for infection, his primary care physician had prescribed doxycycline, for which he had received 5 days of treatment. With the antibiotics, there was no improvement in his legs, so he sought care at the ED. He was then admitted to the hospital due to concern for cellulitis of the lower extremities.

Upon admission, the patient's vital signs were stable, and he had a temperature of 98.7° F, a pulse rate of 86 beats/min, a respiratory rate of 18 breaths/min, a blood pressure of 120/70 mm Hg, and a blood oxygen level of 100% on room air. Initial laboratory studies were significant for creatinine of 3.7 mg/dL, and an estimated glomerular filtration rate via Cockcroft-Gault equation of 19 mL/min. Of note, the patient's baseline creatinine was 2.3-2.5 mg/dL. The urinalysis was significant for protein 10 ml/dL, RBC of 3-5/high-powered field, and rare mucus. The remainder of the laboratory studies are listed in **Table 2**.

Table 2. Initial Laboratory Values of Case #2

Test	Result	Reference range
White blood cell count	11.1 x 10^9/L	4-10.9 x 10^9/L
Hemoglobin	11.4 g/dL	13.5-16.5 g/dL
Platelet count	370 x 10^9/L	135-350 x 10^9/L
Sodium	128 mEq/L	136-145 mEq/L
Chloride	92 mEq/L	101-111 mEq/L
Glucose	273 mg/dL	70-100 mg/dL
Creatinine	3.7 mg/dL	0.7-1.2 mg/dL
BUN	59 mg/dL	6-20 mg/dL
ESR	66 mm/hr	0-20 mm/hr
C3	151 mg/dL	82-167 mg/dL
C4	40 mg/dL	12-38 mg/dL
IgA	464 mg/dL	61-437 mg/dL
Urine blood	Negative	Negative
Urine RBC	3-5/high power field	0-2/high power field
Urine protein	10 mg/dL	Negative mg/dL

Abbreviations: BUN = Blood, urea, nitrogen; ESR = erythrocyte sedimentation rate; RBC = red blood cell

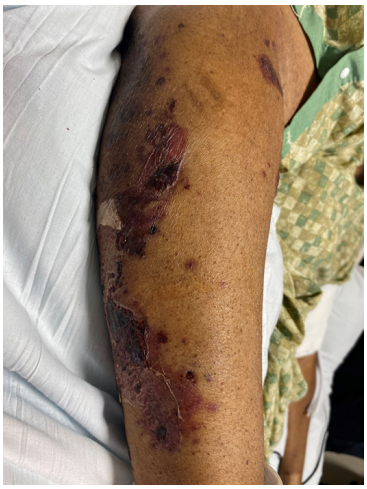

Figure 4. An image of the right arm showed palpable purpura.

The patient was noted to have worsening edema and palpable purpura on the bilateral upper extremities during admission (**Figure 4**). The rash was non-pruritic and was located on the extensor surfaces of his forearms, sparing his hands and palms. The rash had begun several days prior and had steadily worsened since presentation. Autoimmune labs were sent and were negative for antinuclear antibody panel (ANA) including antineutrophil cytoplasmic antibodies (c-ANCA), perinuclear antineutrophil cytoplasmic antibody (p-ANCA), JO-1 antibody, anti-Ro (SS-A) antibody, anti-La (SS-B) antibody, Smith antibody, RNP antibody, Scl-70 antibody, double stranded DNA antibody, chromatin antibody, and centromere B antibody. Significant findings are listed in **Table 2**. The acute hepatitis panel was negative.

A punch biopsy was then performed on the right forearm directly over one of the skin lesions, and then it was sent to pathology. The initial biopsy demonstrated leukocytoclastic vasculitis. At this point, methylprednisolone therapy was administered at 125 mg every 12 hours. The patient then underwent a second punch biopsy, which was sent to an outside facility for IgA immunofluorescence testing. As the initial biopsy was highly suspicious for IgA, he was prescribed 2 weeks of prednisone, 40 mg daily, and then a slow taper over the following 7 weeks, decreasing by 5 mg each week. It was also recommended that the patient have close outpatient follow-up with rheumatology.

After discharge, the IgA immunofluorescence test resulted positive for IgA deposition in the superficial dermal vessels and was consistent with IgA vasculitis (**Figure 5**). One month later, the patient returned to the ED for an unrelated problem, and we found the forearm lesions were healing well. His kidney function had also

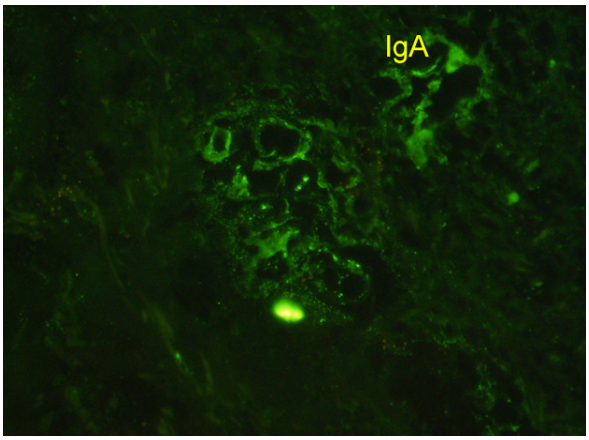

Figure 5. Immunofluorescence staining of the patient's skin biopsy demonstrated granular deposition of IgA in the superficial dermal vessels. Courtesy of the Pathology Department, Medical University of South Carolina.

returned to baseline. It is expected that the patient's wounds have now completely healed. However, no further documentation of the patient's skin condition was available at the time of this paper.

Discussion

Case 1 describes an older patient who developed purpura and worsening renal failure, which led to the diagnosis of IgA vasculitis based on a renal biopsy demonstrating IgA nephropathy and a skin biopsy demonstrating leukocytoclastic vasculitis. The patient was successfully treated with steroid therapy and was lost to follow-up. Case 2 describes an even older patient who developed bilateral lower extremity pain and swelling, worsening renal failure, and purpura, which led to the diagnosis of IgA vasculitis based on skin biopsy demonstrating leukocytoclastic vasculitis and IgA deposition.

IgA vasculitis is the most common vasculitis in childhood and has been extensively studied in children. Childhood IgA vasculitis is often self-limited, with 94% of children experiencing complete recovery.[5] However, IgA vasculitis is much less common in adults, with a broad range of incidence estimates, and tends to be more severe.[6] The median age for IgA vasculitis in adults is 50 years and is more common in men than women.[6] A study of a multi-ethnic cohort from Birmingham, UK, reported that IgA vasculitis was more common in those of Indian subcontinent ancestry when compared to White or Black (predominantly of African-Caribbean ancestry) individuals.[7] IgA vasculitis tends to occur most often during the fall and winter seasons, while the summer has fewer cases reported. A decrease in the frequency of IgA vasculitis during the coronavirus disease 2019 pandemic has been reported, which is most likely associated with mask-wearing and quarantine as well as a decreased circulation of respiratory viruses.[3]

IgA vasculitis presentation differs with age, as older patients exhibit more severe renal and extrarenal manifestations. Necrotic purpura is more likely found in adults and becomes more common with increasing age, while joint manifestations are less frequent.[6] Renal prognosis for adult patients is typically poor.[6] Hetland et al demonstrated that nearly 25% of patients reached renal insufficiency.[8] Risk factors for severe renal failure include age, the presence of macroscopic hematuria, initial renal insufficiency, and proteinuria greater than 1 g/24 hrs.[6] These risk factors were found by unit variant analysis to be prognostic factors for declining renal function.[6] Only initial renal insufficiency and proteinuria were associated with renal insufficiency by multivariant analysis.[6]

Vasculitides are associated with neoplasms and have an incidence of approximately 2-5%.[8] IgA vasculitis is more commonly associated with solid tumors than with hematological malignancies.[8] The gastrointestinal tract, respiratory tract, and urinary tract are the most commonly affected organs, possibly due to their role in IgA production. However, studies have found no evidence for a possible paraneoplastic origin of IgA vasculitis.[8] Given the median age of adult-onset, malignancy screening should be considered in the appropriate adult patients.

IgA vasculitis is a leukocytoclastic vasculitis with an IgA-dominant immune complex deposited within or around the small vessels. The precise etiology of IgA vasculitis remains unknown, but 2 major models of pathogenesis have been proposed. Nephritis associated with IgA vasculitis can be explained using a 4-hit model.[3,9] The first hit involves elevated production of galactose-deficient IgA1. These galactose-deficient globulins bind specific IgA1 autoantibodies (hit 2), forming pathogenic circulating immune complexes comprising the third hit. The fourth hit involves these pathogenic immune complexes depositing in the glomerulus and triggering an inflammatory response.[9] The second model explains the systemic manifestations of IgA vasculitis. The first hit is due to elevated anti-endothelial cell antibody (AECA) levels of the IgA1 subtype, followed by the binding of IgA1-AECA complexes to specific β2 glycoprotein I receptors on vascular endothelial cells (hit 2). This binding induces production of pro-inflammatory cytokines, such as interleukin-8, stimulating neutrophil recruitment (hit 3). Neutrophils are then activated by the interaction of IgA1 and IgA1 Fc alpha receptor I, causing extensive damage to the vascular endothelium via antibody-dependent cellular cytotoxicity, complement-mediated cytotoxicity, and reactive oxygen species. Collec-

tively, these cytotoxicity pathways constitute the fourth hit. This interaction of IgA1 and the IgA1 Fc alpha receptor leads to systemic vascular inflammation information.[3]

The treatment of IgA vasculitis remains controversial and involves a combination of analgesia, antiemetics, hydration, and monitoring for complications.[10] Most evidence is based on studies in the pediatric population. Ronkainen et al evaluated the efficacy of early prednisone therapy, improving renal function and treating extrarenal and renal symptoms in IgA vasculitis.[11] They also showed that prednisone was effective in reducing the intensity of abdominal and joint pain. Prednisone did not prevent the development of renal symptoms but was effective in treating them. Their study concluded that the general use of prednisone in IgA vasculitis is not supported, but patients with disturbing symptoms would benefit from early treatment since the clinical course of disease was not necessarily modified.[11] Another study suggests that methylprednisolone pulse therapy has a positive effect on the outcome of nephropathy in terms of clinical symptoms and histopathological changes, especially if started early during the course of the disease.[12] Given the role of corticosteroids in inhibiting inflammation, it is conceivable that there is a role in disease modification. However, further clinical trials are needed to establish this claim. The patient was given corticosteroids in our first case since he had significant abdominal pain and documented small intestinal involvement through capsule endoscopy. In case 2, the patient started corticosteroids due to his severe lower extremity pain and worsening renal function.

Conclusion

The 2 cases presented in this article demonstrate that IgA vasculitis must be considered within the adult population, and it is not limited to certain ethnic groups. To the best of our knowledge, this case report is the first one to have a person of Native American ancestry with IgA vasculitis. Despite clinical improvement with corticosteroids in our 2 patients, further research is needed to give clarity on the best treatment options for adults with IgA vasculitis. We believe that patients presenting with IgA vasculitis are best managed in a multiple-disciplinary approach, especially those patients with limited improvement despite the initiation of corticosteroids. Our 2 cases should raise awareness of IgA vasculitis in patients with skin rashes and elevated creatinine levels.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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