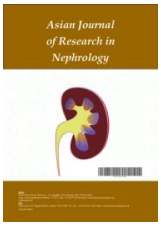

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IgA Vasculitis in a Patient on Dialysis

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Authors' contributions

This work was carried out in collaboration among all authors. Author DKC conceptualized and briefed the case study, got the informed consent signed by the patient, coordinated with the pathologist for the pathology images and reviewed first draft. Author BMC collected the case details from the electronic records, analyzed the data, reviewed literature, wrote the informed consent form, wrote the first draft, edited and finished the final paper ready for submission. Author PP reviewed the case study and provided valuable comments that helped in shaping this paper. Author DP provided the pathology images including the comments on the pathology images for this case study. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Immunoglobulin A vasculitis (IgA Vasculitis), formerly called Henoch Schonlein Purpura (HSP) is a common systemic vasculitis in children. It is 33 times less common in adults than in children. Besides having dermatology manifestations in form of rash, it may affect other organs including kidney (nephritis that can lead to chronic kidney disease), arthritis, arthralgia, abdominal pain, bowel angina and gastrointestinal bleeding.

IgA vasculitis may result in IgA vasculitis nephritis (formerly called HSP nephritis). It shares a lot of similarities with IgA nephropathy, but has some notable differences as discussed later.

IgA vasculitis is rare in chronic kidney disease (CKD) patients on dialysis. We present a case of IgA

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vasculitis in an elderly male with end stage renal disease (ESRD) presumed to be due to diabetic nephropathy (kidney biopsy not available). He developed skin manifestations (rash). Skin biopsy confirmed the presence of IgA vasculitis.

Keywords: IgA vasculitis; immunoglobulin a vasculitis; Henoch Schonlein Purpura; leukocytoclastic vasculitis; IgA nephropathy.

1. INTRODUCTION

Immunoglobulin A vasculitis (IgA vasculitis) occurs in 3-26.7/100,000 infants and children annually. The estimated annual incidence in adults is 0.8-1.8/100,000 adults, about 33 times lesser than infants and children [1]. For reasons unknown, IgA vasculitis in patients with end stage renal disease (ESRD) on maintenance dialysis is very rare. We searched pubmed for IgA vasculitis/Henoch Schoenlein purpura in ESRD patients on dialysis, and we could find only two case reports from the year 1968 onwards. One case was reported by Yoshino J, et al in the year 2007. This 50-year old patient had ESRD due to diabetic nephropathy and was hemodialysis dependent [2]. Another case was reported by Lamikanra O, et al in 2019. This 63-year old patient had ESRD due to hypertension and was on maintenance hemodialysis [3].

We are reporting a case of IgA vasculitis in an elderly male with ESRD presumed to be due to diabetic nephropathy (not biopsy proven). There is a possibility that etiology of chronic kidney disease (CKD) in this patient could be due to IgA Nephropathy. IgA nephropathy and IgA vasculitis with nephritis have some shared features as discussed later in this case report.

2. CASE REPORT

A 61-year-old man with history of diabetes mellitus with diabetic retinopathy, hypertension, benign prostatic hypertrophy, recurrent pyelonephritis and chronic kidney disease (CKD) presumed to be due to diabetes mellitus (kidney biopsy was not done as patient had recurrent pyelonephritis), on maintenance hemodialysis for the past one and a half years, presented to the emergency department with three days of itchy rash on both lower limbs (shown in Fig. 1), and dull abdominal pain associated with nausea and vomiting and loose stools.

There was no history of fever, chest pain, palpitations, syncope, breathlessness, or any other systemic symptoms. There was no history suggestive of respiratory infection or gastrointestinal infection immediately preceding to this illness. Patient had no history of smoking, alcohol abuse or recreational drug abuse.

His regular medications included amlodipine, metoprolol, moxonidine, tamsulosin and dutasteride combination, ferrous ascorbate and folic acid combination, multivitamins, furosemide, pantoprazole, and parentally administered erythropoietin alpha, ferric carboxymaltose and levocarnitine.

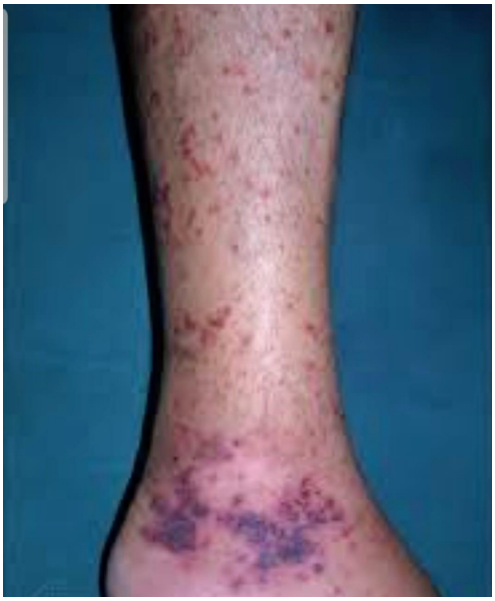

Fig. 1. Erythematous palpable purpura in IgA vasculitis

On physical examination the patient was hypertensive (blood pressure 160/80 mm Hg), tachycardic (pulse 114/min), tachypneic, hypoxic with an oxygen saturation of 90%. He was afebrile. Systemic examination showed bilateral basal crepitations in chest. He had painful palpable purpura in both lower limbs (Fig. 1). The rash was confluent on the ankles with several necrotic areas.

His blood sugar level was 856 mg/dl. Venous blood gas analysis showed pH: 7.359; pO2: 44.5 mm Hg; pCO2: 42.6 mm Hg; HCO3: 22.8 milliequivalents per liter (mEq/L); lactate: 1.5 mmol/L. Hemoglobin was 11.7 gm/dl. A complete blood count revealed leukocytosis (total leukocyte count: 16,700 per microliter) with 88% neutrophils, 5.8% lymphocytes, 5.8% monocytes,

0.2% basophils, and 0.2% eosinophils. Platelet counts were normal. C- reactive protein was elevated (8.99 mg/dl). His serum electrolytes were as follows: Sodium 123 mmol/L, potassium 4.7 mmol/L, chloride 84 mmol/L. Serum albumin 1.8 gm/dl. Blood urea: 101 mg/dl, serum creatinine 5.33 mg/dl. Serum bilirubin and liver enzymes were normal.

Patient was admitted in intensive care for aggressive management of the blood sugar level. While his condition stabilized, we continued evaluating the cause of rash. Anti-streptolysin-O titer was found to be negative. Serum C3 complement was low (79.7 mg/dl, normal range 90-180 mg/dl), C4 complement was normal (39.1 mg/dl, normal range 10-40 mg/dl).

Suspecting IgA vasculitis, dermatologist's consultation was taken, and punch biopsy of skin was done.

Skin biopsy report is as described in Table 1. The light Microscopy (Fig. 2) and Immunofluorescence (Fig. 3) are also given below.

Table 1. Skin biopsy

Light microscopy (see Fig. 2)	Epidermis: focal spongiosis and neutrophilic exocytosis. Dermis: perivascular infiltrate of neutrophils and lymphocytes with intramural extension and nuclear dust. Endothelial cell swelling and fibrinoid necrosis of small vessel walls present. Extravasated RBCs seen.
Direct immunofluorescence (see Fig. 3)	Positivity for IgA (4+), C3 (2+), and fibrinogen (4+) in the papillary dermal blood vessels. IgG, IgM, and c1q negative. No deposits found in the epidermis.
Impression	Leukocytoclastic vasculitis with IgA deposits in the papillary dermal vessels consistent with IgA vasculitis (Henoch Schonlein Purpura).

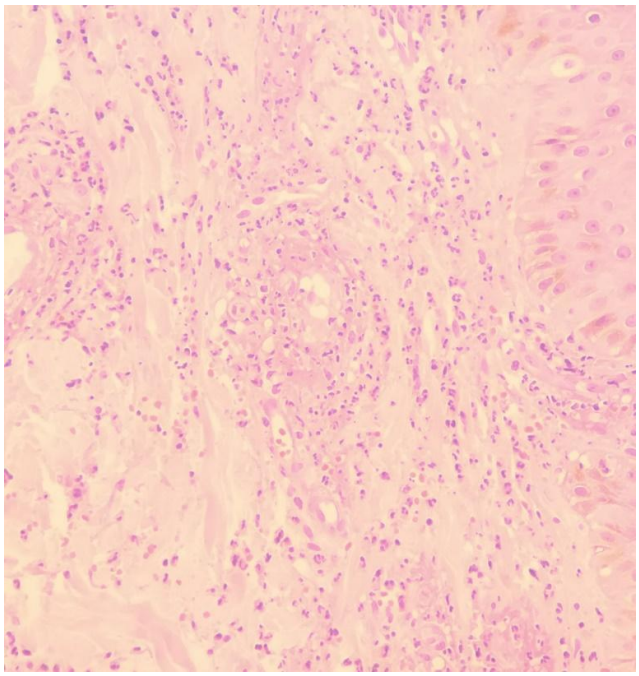

Fig. 2. Light microscopy, skin biopsy

Epidermis: focal spongiosis and neutrophilic exocytosis. Dermis: perivascular infiltrate of neutrophils and lymphocytes with intramural extension and nuclear dust. Endothelial cell swelling and fibrinoid necrosis of small vessel walls present. Extravasated red blood cells (RBCs) seen

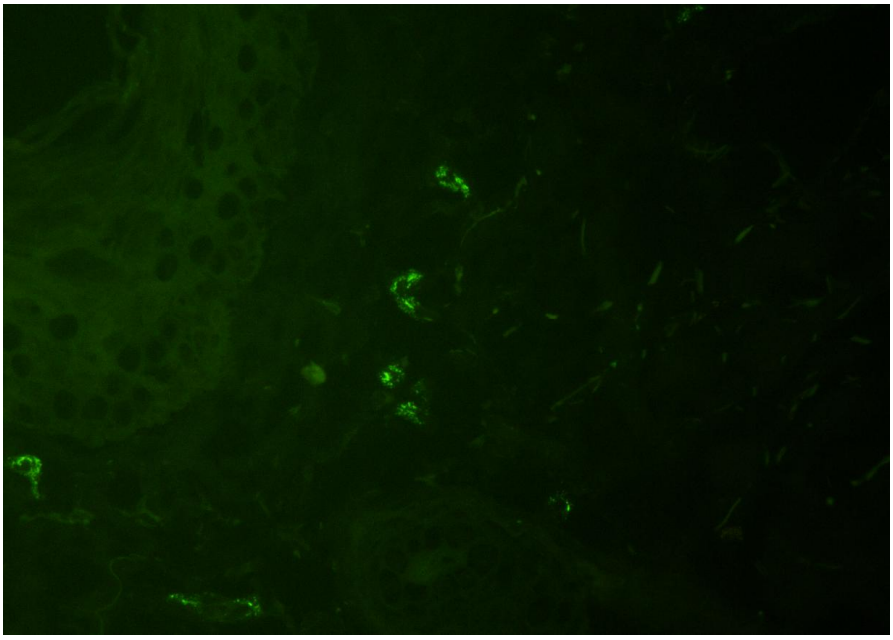

Fig. 3. Direct immunofluorescence, skin biopsy

Coarse granular deposits of antibodies to IgA in the papillary dermal vessels. There was also Complement 3 (C3), and fibrinogen deposits in the papillary dermal vessels (not in the image)

The skin biopsy confirmed that the patient was having IgA vasculitis. He was managed with oral prednisolone (started at 25 mg per day, slowly tapered to 10 mg per day maintenance dose in 10 days), beclomethasone lotion, oral anti-histamines and moisturizing cream. The rash showed improvement over one month of treatment and resolved completely in 2 months.

3. DISCUSSION

Genetic predisposition to IgA vasculitis is supported by familial occurrence of cases [4]. Human leukocyte antigen (HLA) system located on short arm of chromosome six, plays a critical role. HLA–DRB1*01, HLA-B*41:02 may be associated with occurrence of IgA vasculitis, whereas HLA–DRB1*03 may have a protective effect [4-6].

IgA vasculitis in patients on dialysis is very rare. Hiroyuki Ueda, et al reported that 23 patients with biopsy proven IgA vasculitis with nephritis in their study. Thirteen of these 23 patients were elderly (age ≥60 years). Twelve of these 13 elderly patients had one or more comorbidities (including hypertension, diabetes mellitus, cardiovascular disease, CKD, and malignancy). CKD was found in 4 patients among the 12 patients with comorbidities. None of these four patients were on long term maintenance dialysis (dialysis therapy dependent) either before or after the study period, though two of these patients needed temporary dialysis due to temporary worsening of renal functions during the study (median follow up of 15 months, range 3-80 months) [7]. Pubmed search for IgA vasculitis/Henoch Schoenlein purpura in ESRD patients on dialysis revealed only two case reports from the year 1968 onwards. One case was reported by Yoshino J, et al in the year 2007. This 50-year old patient had ESRD due to diabetic nephropathy and was hemodialysis dependent [2]. Another case was reported by Lamikanra O, et al. in 2019. This 63-year old patient had ESRD due to hypertension and was on maintenance hemodialysis [3]. This suggests that IgA vasculitis in CKD patients on dialysis is rare.

The pathophysiologic mechanisms that could account for so rare occurrence of IgA vasculitis in CKD patients on dialysis is unknown. We know that end stage kidney disease (ESRD) is associated with dysfunction of both innate and adaptive immunity. Alteration of costimulatory molecules CD80 and CD86 results in dysfunction of antigen presenting cells [8]. This may affect release of cytokines affecting (decreasing) chemotaxis of leukocytes, less incidence of damage to endothelial walls, and decreased migration of these leukocytes into the tissues, and poorer response to several antigens in CKD

patients [9]. We hypothesize that the altered pathophysiology of immune system in ESRD may be responsible for decreased incidence of IgA vasculitis in patients on dialysis. However, this is an area for further study.

4. LEUKOCYTOCLASTIC VASCULITIS

Leukocytoclastic vasculitis, also known as cutaneous small vessel vasculitis and hypersensitivity vasculitis, is characterized by erythema and palpable purpuric (non-blanching) rash mainly on the dependent areas like feet or lower limbs [10,11]. Papules, pustules, nodules, blisters, and ulceration may occur. Extracutaneous manifestations include nephritis, pleuritis, pulmonary infiltrates, acute abdomen, involvement of cranial nerves, convulsions, headache, epicarditis and myocarditis [10]. Leukocytoclastic vasculitis usually follows a respiratory infection or drug intake [10,11]. Triggering antigens; for example, a bacterium, virus or a drug; may incite an immunological response. Antigen-antibody complex deposition occurs in the walls of small vessels leading to vasculitis.

Investigations may show elevated erythrocyte sedimentation rate, leukocytosis, decreased serum complement titer, and hypergammaglobulinemia [10]. Investigations may detect immune complexes.

Skin biopsy is diagnostic. Biopsy may show perivascular neutrophilic infiltration into small dermal vessels (arterioles, capillaries and venules) [10,11]. The neutrophils degranulate, and then undergo death and breakdown (leukocytoclasia), thereby releasing nuclear debris or nuclear dust [11]. Fibrinoid degeneration of the vascular walls characterized by fibrin deposition in and around vessel walls, and leakage of erythrocytes occur [10,11]. The pathologic lesions are found in the whole dermis layer [10]. Direct immunofluorescence may reveal vascular deposition of immune complexes in 92% of the skin biopsy samples. Immune complex deposition occurs early in the course of the disease (as early as the first few hours after the onset of cutaneous lesions). The destruction and elimination of the immune complexes begins early too (within 48 hours of onset of lesions). This means that skin biopsy done early may have higher diagnostic yield than the biopsy done after 24 to 48 hours of the onset of lesions. Complement component 3 (C3) deposition occurs more frequently and persists longer than immunoglobulins [11].

Treatment consists of identifying, treating, and eliminating the cause or trigger (like drugs including penicillin, or infection with hemolytic streptococcus or a virus). Symptomatic pain relief through non-steroidal anti-inflammatory drugs (NSAIDS) and use of dapsone (DDS) are helpful. Adequate bed rest, elevation of lower limbs (if lower limbs are affected) is advised. Severe cases with systemic symptoms may need systemic corticosteroids and immunosuppressants [10].

5. IgA VASCULITIS

IgA vasculitis (previously called Henoch-Schönlein purpura) is a type of leukocytoclastic vasculitis [10,12]. Clinical features include palpable purpura (mostly in lower limbs), arthritis, abdominal pain, nausea, vomiting, hematemesis, malena, and nephritis. Pathologically, it forms a part of the spectrum of leukocytoclastic vasculitis. The pathologic findings are localized in the upper layer of dermis. Scattered nuclear fragments or nuclear dust, fibrinoid degeneration are found in the subpapillary vessels in the upper layer of dermis. Direct immunofluorescence reveals deposition of IgA [10]. IgA1 subclass deposition occurs predominantly, as shown by C.A Egan, et al. These investigators found that out of 28 patients studied, all 28 patients showed deposition of IgA1, only 1 patient showed deposition of IgA2 [13]. Renal biopsy (when renal symptoms occur) usually shows crescentic glomerulonephritis [10].

There is more systemic involvement (including gastrointestinal and renal involvement) and worse prognosis in IgA vasculitis when compared with hypersensitivity vasculitis [11]. Use of corticosteroids or cytotoxic drugs is much more common in patients with IgA vasculitis than in hypersensitivity vasculitis, as expected given the more severe nature of IgA vasculitis [14]. Researchers have claimed that even though hypersensitivity vasculitis and IgA vasculitis have similar cutaneous involvement, they should be considered as two separate entities.

6. IgA VASCULITIS WITH NEPHRITIS (IgA- VN) AND IgA NEPHROPATHY

Though IgA vasculitis with nephritis (IgA-VN) has several similarities with IgA nephropathy, there are some notable differences (See Table 2). Extra-renal manifestations occur in IgA-VN but not in IgA Nephropathy [9].

Table 2. Differences between IgA vasculitis with nephritis and IgA nephropathy

Characteristics	IgA Vasculitis with Nephritis	IgA Nephropathy
Extra-renal manifestations	Yes	No
Age of onset	Usually in children	Usually in older teens and adults
Association with hypersensitivity	Yes.	No
Histology: IgA deposits, endocapillary proliferation, and crescent formation	Mesangial IgA deposits present, but IgA deposits in capillary walls may predominate. Extensive IgA deposits in capillary walls results in severe diffuse endocapillary proliferation and/or crescent formation.	Predominant mesangial IgA deposits in all glomeruli. Capillary wall IgA deposits may occur. Extensive IgA deposits in capillary walls, if present, results in severe diffuse endocapillary proliferation and/or crescent formation.

Reference: Davin J.C, Berge I.J.T, Weening J.J. What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis? Kidney International. March 2001;59(3):823–834

Predominant intraglomerular mesangial IgA1 deposits are found more commonly in IgA nephropathy as compared with IgA-VN. IgA deposits in capillary walls may also occur in both the diseases but are more commonly found in IgA-VN. These capillary wall IgA deposits (subepithelial and subendothelial) are more commonly found in IgA-VN, and may even predominate mesangial IgA deposits in this disease. Glomerular deposits of IgG, IgM, C3 and alternative complement pathway components are found in both IgA-VN, and IgA nephropathy [9].

7. CONCLUSION

Since this patient did not have any cutaneous manifestations before this episode (no IgA vasculitis earlier) that could have led to development of CKD, it is unlikely that CKD in this patient is due to IgA-VN. However, since IgA nephropathy does not present with cutaneous manifestations unlike IgA vasculitis with nephritis, this patient may be having IgA nephropathy.

IgA vasculitis in CKD population on dialysis is very rare. The reason for so rare occurrence of IgA vasculitis in patients on dialysis is unknown. ESRD is associated with dysfunction of both innate and adaptive immunity. Alteration of costimulatory molecules CD80 and CD86 results in dysfunction of antigen presenting cells [8]. This may affect release of cytokines affecting (decreasing) chemotaxis of leukocytes, less incidence of damage to endothelial walls, and decreased migration of these leukocytes into the tissues [9,15]. We hypothesize that this may account for poorer response to several antigens (hence decreased incidence of hypersensitivity) in CKD patients. We further hypothesize that the altered pathophysiology of immune system in ESRD, with poorer response to several antigens, may be responsible for decreased incidence of IgA vasculitis in patients on dialysis. However, this is an area that needs to be explored.

CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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