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Case report

Systemic IgA Vasculitis withs Severe Kidney Involvement Associated with Human Immunodeficiency Virus Infection.

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Patient Consent

The authors declare that they have obtained signed written consent from the patient discussed in the report.

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Introduction:

In the highly active antiretroviral treatment era, human immunodeficiency virus (HIV) infection has become a chronic condition with multiple associated complications including kidney and rheumatologic diseases. Patients infected with HIV can show a spectrum of kidney disease including HIV-associated nephropathy (HIVAN), HIV-associated immune complex kidney disease (HIVICD), thrombotic microangiopathy, drug induced nephrotoxicity or other disease that are associated with abnormal immune function and super infections [1]. Although antiretroviral medications can increase life expectancy in HIV patients, it is also associated with increasing risk of kidney disease and decline in kidney function [2]. IgA nephropathy is the third most common

HIVICD and was seen in 9% of patients in an HIV clinical cohort study [3]. Presentation of IgA nephropathy as a component of IgA vasculitis (IgAV) [Henoch-Schonlein purpura (HSP)] is rare in HIV infected adults and it has only been reported in a few case reports [4-6]. Here, we present a case of systemic IgAV with severe kidney involvement in the setting of HIV and review the treatment challenges.

Case:

55-year-old man with a 10-year history of HIV presented with 2 weeks of progressively increasing bilateral lower extremity edema along with tender, palpable purpuric skin lesions and diffuse joint pain, and mild abdominal pain and loose bowel movements for 1 week.

He reported active smoking with a history of substance abuse in the past but denied recent IV drug use. Patient was off his antiretroviral therapy for 1 year and resumed Elvitegravir, Cobicistat, Emtricitabine and Tenofovir alafenamide combination therapy (Genvoya) and Trimethoprim-sulfamethoxazole for Pneumocystis jiroveci pneumonia (PJP) prophylaxis 6 weeks before presentation. He reported treatment with the same regimen in the past without any complications. His physical examination was remarkable for a non-blanching palpable purpura circumferentially around his ankles and extending up to his mid-calves with bilateral pitting edema of his lower extremities (Fig 1).

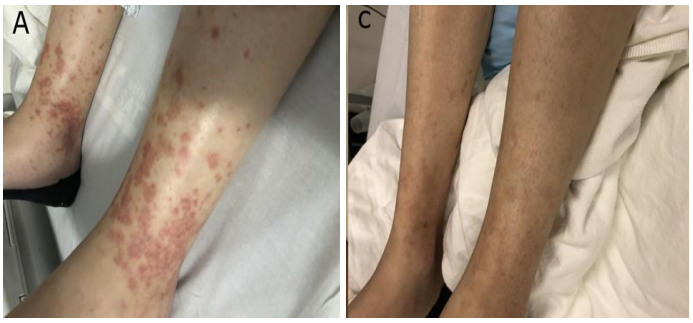

Figure 1. Initial presentation of non-blanching palpable purpura circumferentially around bilateral ankles (A). Prior to discharge, complete resolution of ankle rash (B).

He was found to have acute kidney injury with serum creatinine 4.74 mg/dL (baseline 1.08 mg/dL), BUN 71mg/dL, microscopic hematuria, and nephrotic range proteinuria with protein to creatinine ratio of 5.4 mg/g and more than 12 grams protein on 24-hour urine collection. CRP (5.4 mg/dl) and ESR (71 mm/hr) were elevated. CMV DNA PCR was positive. His CD4 count was 165 with an HIV viral load of 743 copies/ml. c-ANA, p-ANCA, ANA and RF were negative. Serum protein electrophoresis showed no monoclonal bands and C3/C4 were within normal range.

A skin biopsy was performed (Fig 2), which showed acute leukocytoclastic vasculitis with focal vascular necrosis/fibrinoid necrosis with mild leukocytoclastic and scattered eosinophils. On direct immunofluorescence, superficial granular vascular staining with IgA and C3 were seen, suggestive of Henoch-Schonlein purpura (HSP)/IgA vasculitis. The presence of eosinophils on skin biopsy raised the possibility of drug related reactions. All of his home medications including Genvoya and Bactrim were placed on hold and high dose steroids were started with significant improvement in his skin lesions on day 2 of admission. His serum creatinine initially trended down to 2.89 mg/dL on day 3; however, it started to slowly increase despite treatment.

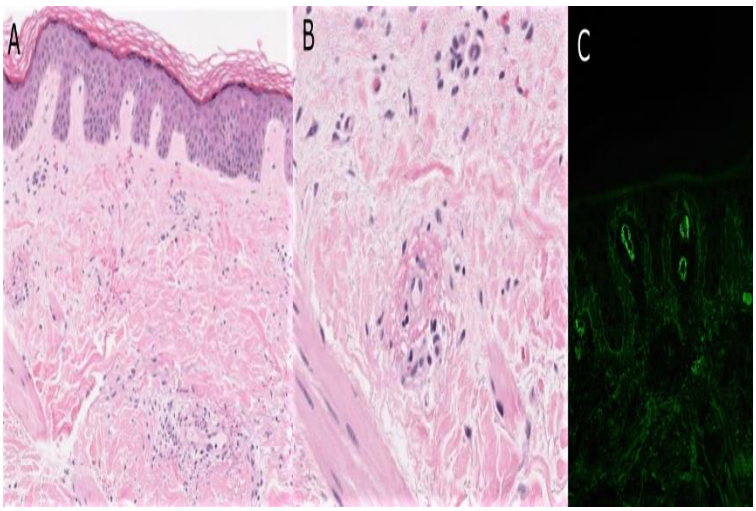

Figure 2. Skin biopsy consistent with vascular necrosis with adjacent neutrophilic inflammation, leukocytoclasis, and extravasated red blood cells consistent with leukocytoclastic vasculitis (A (10x), B (20x), H&E stain). Immunofluorescence microscopy demonstrated granular deposition with IgA in the superficial papillary dermal blood vessels, consistent with IgA vasculitis (C).

Given the continued acute kidney injury, a kidney biopsy was performed (Fig 3). The kidney biopsy was composed of cortex containing 43 glomeruli (15 globally sclerotic) and demonstrated a diffuse proliferative and focal necrotizing/crescentic

glomerulonephritis including ~45% glomeruli involvement by cellular crescents. There were foci of capillary loop necrosis and basement membrane disruption. Most glomeruli exhibit segmental to global endocapillary hypercellularity as well as prominent mesangial and large wire-loop type capillary loop deposits. There was extensive tubulointerstitial inflammation composed of lymphocytes, histiocytes, plasma cells and eosinophils associated with acute tubular injury and mild interstitial fibrosis and tubular atrophy. There was moderate to severe arterio/arteriolosclerosis without arteritis or thrombosis.

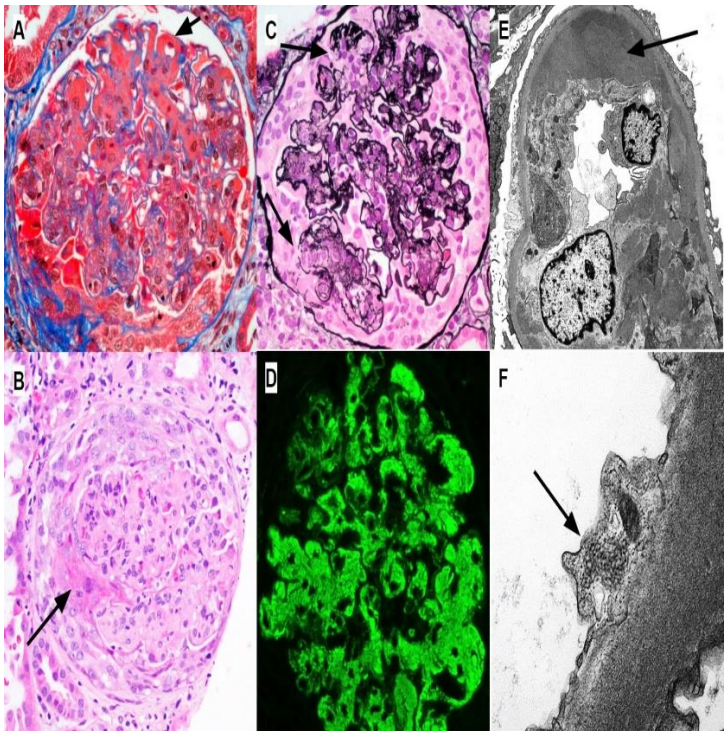

Figure 3. Kidney biopsy demonstrated severely active IgA dominant immune complex glomerulonephritis with massive IgA deposits and necrotizing crescents. Light microscopy demonstrated (A) large mesangial and wire-loop like subendothelial deposits (arrow) highlighted on trichrome stain, (B, H&E stain) cellular crescents with fibrinoid necrosis (arrow) of glomerular capillary loops and, (C) glomerular capillary loop disruption (arrows) highlighted on jones silver stain (all light microscopy images are 400x). (D) Immunofluorescence microscopy demonstrated bright granular to confluent IgA dominant glomerular staining (400x). (E) Electron microscopy demonstrated granular and large subendothelial (arrow) and mesangial deposits. (F) Scattered tubuloreticular inclusions were present.

Immunofluorescence studies demonstrated diffuse global granular glomerular mesangial and capillary wall staining with IgG (2-3+), IgA (4+), IgM (trace), C3 (4+), kappa (2-3+) and lambda (4+) light chains without significant extra-glomerular staining. Electron microscopy studies demonstrated numerous large immune complex deposits in mesangial regions, subendothelial spaces, and rarely in subepithelial spaces. Early double capillary wall contour formation was present. Subepithelial "hump-like" deposits or mesangial notch region deposits were not present. Podocytes exhibited extensive foot process effacement. Tubuloreticular inclusions were present.

The final diagnosis was IgA dominant immune complex-mediated glomerulonephritis.

Given evidence of active crescents, severe proteinuria, and rising serum creatinine, the patient was started on Cyclophosphamide in addition to steroids along with Atovoquone for PCP prophylaxis and Valganciclovir for CMV treatment per ID recommendations. Antiretroviral therapy was not initiated given decreasing GFR and treatment of acute GN.

Patient's nadir serum creatinine was 3.39 mg/dL and he was discharged on cyclophosphamide and prednisone. Two weeks later the patient developed weight gain with recurrence of bilateral lower extremity edema and dyspnea on exertion. Patient was started on ethacrynic acid given his history of Bactrim allergy with improvement of lower extremity edema. Labs were significant for an up trending serum creatinine to 3.74 mg/dL, a BUN of 82mg/dL, persistent microscopic hematuria and spot urine protein to creatinine ratio of 10.9 mg/g.

Patient subsequently was unable to continue cyclophosphamide for 3 weeks due to insurance authorizations. Patient was restarted on anti-viral therapy with Abacavir, Dolutegravir, and Lamivudine combination therapy over one month after hospitalization. On 6-week follow-uplabs, serum creatinine continued to uptrend to 4.0 mg/dL with a BUN of 71 and microscopic hematuria on urinalysis. Care was further complicated by poor adherence and missing follow up appointments.

He presented 18 months later with weakness and recurrent falls. He was not taking any HIV medication or immunosuppression for 1 year. His serum creatinine was 5.32 mg/dl, BUN 58mg/dl and urine protein to creatinine ratio of 5.39 mg/g. At this point, repeat kidney

biopsy was deferred given suspicion of chronic changes in the setting of medication non-adherence that will not change the management.

Discussion:

IgA vasculitis (IgAV) is characterized by leukocytoclastic vasculitis and small vessel involvement in the skin, GI system and kidneys with IgA immune complex deposition. IgAV is uncommon in adults and has only been reported in rare cases in association with HIV [4-6]. Zhang et al studied rheumatological manifestations in 98 patients with HIV with IgAV occurring in only 2 patients [7]. Our patient presented with palpable purpura, abdominal pain and leukocytoclastic vasculitis with IgA and C3 deposits on skin biopsy that was consistent with IgAV diagnosis. IgAV was reported mostly in patients who were off treatment or with interruption in the antiretroviral therapy or had low CD4 count [8,9]. However, in our patient, although he had an interruption in HIV treatment, the IgAV symptoms started 6 weeks after restarting the medications that would suggest a possible role of immune reconstitution syndrome.

IgA nephropathy has been reported in association with multiple infections including HIV and is the third most common form of HIV-associated immune complex kidney disease (HIVICD) [1,3,10]. Circulating immune complexes composed of idiopathic IgA antibodies and anti-HIV antibodies of different classes were reported in HIV associated IgA nephropathy. In the UK CHIC cohort study, IgA nephropathy was associated with antiretroviral therapy but it was not associated with CD4 cell count or HIV viral load [11]. Dysregulation in the immune system associated with HIV infection in response to continued production of anti-HIV antibodies or a response to other opportunistic infections and antigen presentation associated with HIV may be a possible mechanism of IgA nephropathy in HIV patients [1,11,12].

In our patient, the kidney biopsy showed IgA dominant immune complex glomerulonephritis. The histologic and immunophenotypic features were not typical for a primary IgA nephropathy given the large wire-loop type subepithelial deposits, bright IgG staining, and the presence of tubuloreticular inclusions and as such the diagnosis of an HIV associated IgA nephropathy was favored. The differential diagnosis included infection-related IgA glomerulonephritis not necessarily related to HIV such as streptococcus-associated glomerulonephritis. However, our patient did not have any signs or symptoms of acute infection or recent infection history. The presence of eosinophils on skin biopsy raised the possibility of drug reaction; however, drug induced glomerulonephritis was less likely based on the biopsy results.

There is limited data on the treatment of IgA nephropathy and IgAV in the setting of HIV infections. Antiretroviral therapy and decreased viral load have shown some improvement in patients with IgAV [5,6]. Improvement in GFR and reduction in proteinuria were observed in patients with HIVICD after starting antiretroviral therapy [11]. In addition, pulse steroid therapy and colchicine resulted in complete remission in a case report of IgAV and IgA nephropathy in thesetting of HIV [4]. In a study by Tumlin JA et al. methylprednisolone and cyclophosphamide treatment in a patient with IgA nephropathy and more than 10% crescents in biopsy showed a significant improvement in proteinuria and stabilized serum Cr with reduced cellular crescent and endocapillary proliferation with minimized cortical scarring [13]. However, immunosuppressive therapy in HIV associated IgA nephropathy remains an area with concern given these patients' immunocompromised status [1]. A retrospective cohort study of 21 patients diagnosed with HIVAN and progressive kidney failure treated with prednisone versus no steroid therapy showed no difference in incidence of serious infections between the 2 groups [14].

Despite improvement in dermal symptoms in response to high dose steroid therapy (Fig1B), his kidney function continued to decline even with addition of cyclophosphamide to his regimen. Further confounders in this case included insurance challenges and patient's noncompliance. This case demonstrates that acute IgAV with kidney and dermal involvement in the setting of HIV can progress rapidly to advanced CKD and ESKD within a few months if it remains untreated.

The treatment of IgAV in HIV infected patients is not well defined and is based on case reports. Severe IgAV in adults is often treated with immunosuppressive treatments with limited evidence of effectiveness. Thus, further studies and collaborative discussions are greatly needed to evaluate optimal therapy for HIV-positive patients with IgA nephropathy and IgAV.

References:

1. Nobakht E, Cohen SD, Rosenberg AZ, Kimmel PL (2016) HIV-associated immune complex kidney disease. NatRev Nephrol 12: 291-300.
2. Kidney Diseases Associated with Human Immunodeficiency Virus Infection.Cohen SD, Kopp JB, Kimmel PL. N Engl J Med (2017) 377: 2363-2374.
3. Foy MC, Estrella MM, Lucas GM, Tahir F, Fine DM, et al. (2013) Comparison of Risk Factors and Outcomes in HIV Immune Complex Kidney Disease and HIV-Associated Nephropathy. Clin J Am Soc Nephrol 8: 1524 LP -1532.
4. Contreras-Chavez P, Anampa-Guzmán A, Henao J, Fernandez R, Saad P (2019) Not your Typical Rash: ACase of IgA Nephropathy in the Setting of HIV. Cureus 11.
5. Sugimoto T, Tsuda A, Kito K, Uzu T, Kashiwagi A (2008) Henoch-Schönlein purpura in a patient with human immunodeficiency virus infection. Rheumatol Int 28: 615-616.
6. Hidaka H, Okada T, Matsumoto H, Yoshino M, Nagaoka Y, et al. (2003) [Henoch-Schönlein purpura nephritis in a atient infected with the human immunodeficiency virus]. Nihon Jinzo Gakkai Shi 45: 387-392.
7. Zhang X, Li H, Li T, Zhang F, Han Y (2007) Distinctive rheumatic manifestations in 98 patients with human immunodeficiency virus infection in China. J Rheumatol 34: 1760-1764.
8. Bunupuradah T, Puthanakit T, Pancharoen C, Butterworth O, Phanuphak P, et al. (2008) Henoch-Schönlein purpura and thrombocytopenia after planned antiretroviral treatment interruption in a Thai girl with HIV infection. Int J Infect Dis 13: 31-33.
9. Journal M. MEDITERRANEAN JOURNAL strategies (2017) 28: 4-12.
10. Rollino C, Vischini G, Coppo R (2016) IgA nephropathy and infections. J Nephrol 29: 463-468.
11. Booth JW, Hamzah L, Jose S, Horsfield C, O'Donnell P, et al. (2016) Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. Nephrol Dial Transplant 31: 2099-2107.
12. Kimmel PL, Phillips TM, Ferreira-Centeno A, Farkas-Szallasi T, Abraham AA, et al. (1992) Brief report: idiotypic IgA nephropathy in patients with human immunodeficiency virus infection. N. Engl. J. Med 327: 729-730.
13. Tumlin JA, Lohavichan V, Hennigar R (2003) Crescentic, proliferative IgA nephropathy: Clinical and histological response to methylprednisolone and intravenous cyclophosphamide. Nephrol Dial Transplant 18: 1321-1329.
14. Eustace JA, Nuermberger E, Choi M, Scheel PJ Jr, Moore R, et al. (2000) Cohort study of the treatment of severe HIV-associated nephropathy with corticosteroids. Kidney Int 58: 1253-1260.