Abstract

Human immunodeficiency virus (HIV)-positive individuals are at an increased risk for kidney diseases, including HIV-associated nephropathy (HIVAN), focal segmental glomerulosclerosis (FSGS), HIV immune complex disease of the kidney (HIVICK), and acute tubular necrosis (ATN). Non-modifiable factors such as age and genetics, as well as modifiable factors such as illicit drug use and compliance, define the progression to renal failure. The patient is a 64-year-old African American male with HIV, treated latent syphilis, chronic kidney disease stage 3a, and cocaine use disorder who presented with shortness of breath, bilateral lower extremities swelling, and fatigue with normal vitals and a physical exam remarkable for bibasilar inspiratory crackles with peripheral edema. Laboratory tests showed creatinine (Cr) of 2.23 mg/dL with a baseline of 1.5 mg/dL, albumin of 1.8, blood natriuretic peptide (BNP) of 667.88, and lipidemia. His urine was remarkable for proteinuria and microalbuminuria in the presence of cocaine. Immunofixation electrophoresis showed a marked increase in IgG and IgM, free lambda, and free kappa/free lambda ratio with HIV viral load of 39,400 copies/mL, absolute CD4 count of 56, and an acute hepatitis B panel. Renal biopsy confirmed HIVAN with FSGS accompanied by collapsing features, HIVICK, and ATN. The patient was subsequently started on highly active antiretroviral therapy (HAART) with prophylactic antibiotics and close monitoring.

Introduction

Human immunodeficiency virus type 1 (HIV-1) seropositive patients are at an increased risk for kidney diseases, including HIV-associated nephropathy (HIVAN), focal segmental glomerulosclerosis (FSGS), HIV immune complex disease of the kidney (HIVICK), and acute tubular necrosis (ATN). Non-modifiable factors such as age and genetics, as well as modifiable factors such as illicit drug use and compliance, define the progression to renal failure. The most common cause of chronic renal failure in HIV-1-seropositive patients is HIVAN, almost exclusively seen in black patients. It was primarily described in 1984 by Rao et al. [1-3]. In this article, we present the case history of a 64-year-old African American male with HIV who presented with nephropathy and was found to have HIVAN, HIVICK, and ATN.

Case Presentation

The patient is a 64-year-old African American man with HIV, treated latent syphilis, chronic kidney disease stage 3a, and cocaine use disorder who presented with progressive, exertional shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, bilateral lower extremities swelling, and fatigue of a couple of weeks duration. Review of systems was unremarkable. He reported non-compliance to HIV medications for the past three years (diagnosed 17 years ago) and had no scheduled medications. The patient was vitally stable with a physical exam remarkable for bibasilar inspiratory crackles and +2 pitting edema on lower extremities. Laboratory tests (Table 1) showed normal hemoglobin, creatinine (Cr) of 2.23 mg/dL with a baseline of 1.5 mg/dL, blood urea nitrogen (BUN) of 27 with a glomerular filtration rate of 36 mL/min, albumin of 1.8 g/dL, blood natriuretic peptide (BNP) of 667.88 ng/mL, and lipidemia. His urine was remarkable for proteinuria with a microalbumin/creatinine ratio of 3364.2 mcg/mg in the presence of cocaine. Immunofixation electrophoresis showed a marked increase in IgG and IgM, free lambda, and free kappa/free lambda ratio with HIV viral load of 39,400 copies/mL with an absolute CD4 count of 56. Hepatitis B surface antigen and hepatitis B e antigen were positive. Echocardiography showed diastolic heart failure with preserved ejection fraction and the patient was started on intravenous furosemide for symptomatic relief.

Keywords:

- hiv associated nephropathy (hivan)
- hiv-associated immune complex kidney disease (hivick)
- non collapsing focal segmental glomerulosclerosis (fgs)
- polyclonal gammopathy
- light chains
- nephropathy
- proteinuria
- immune-complex kidney disease
- acute tubular necrosis (atn)
- human immunodeficiency virus-1(hiv-1)

Categories:

- Internal Medicine
- Infectious Disease
- Nephrology
| Preliminary Laboratory work | Value     | Reference range      |
|-----------------------------|-----------|----------------------|
| Hemoglobin                  | 13.7 g/dl | 14.0-16.5 g/dl       |
| Creatinine                  | 2.23 g/dl | 0.70-1.30 g/dl       |
| BUN                         | 27 mg/dl  | 7.18 mg/dl           |
| Albumin                     | 1.8 g/dl  | 2.9-4.4 g/dl         |
| Cholesterol                 | 218 mg/dl | <200 mg/dl           |
| LDL Cholesterol             | 141 mg/dl | 60-130 mg/dl         |
| BNP                         | 667.88 ng/ml | 0.01-0.045 ng/ml         |

| Urine Studies               | Value     | Reference range      |
|-----------------------------|-----------|----------------------|
| White Blood Count           | 11-15/ High Power Field | 0-5/ High Power Field |
| Urine Protein               | 100 mg/dl | Negative             |
| Random Creatinine           | 29.10 mg/dl | 30-115 mg/dl         |
| Random Microalbumin         | 979.0 mg/dl | <30 mg/dl           |
| Creatinine                  | 29.1 mg/dl | 30-115 mg/dl         |
| Microalbumin/Creatinine     | 3364.2 mcg/mg | 0-30 mcg/mg CR    |
| Cocaine Screen             | Positive  | Negative             |

| Immunology                  | Value     | Reference range      |
|-----------------------------|-----------|----------------------|
| Immunofluorescence IgG      | 4085 mg/dl | 603-1613 mg/dl       |
| Immunofluorescence IgA      | 216 mg/dl  | 61-437 mg/dl         |
| Immunofluorescence IgM      | 469 mg/dl  | 20-172 mg/dl         |
| Anti-Proteinase 3           | <3.5 U/ml | 0-3.5 U/ml           |
| Atypical p-ANCA             | <1:20 titer | <1:20 titer         |
| p-ANCA antibody             | <1:20 titer | <1:20 titer         |
| Myeloperoxidase antibody    | <9 U/ml    | 0-9 U/ml             |
| ANCA                        | 1:40 titer | <1:20 titer         |
| Complement C3               | 112 mg/dl  | 90-180 mg/dl         |
| Complement C4               | 19.2 mg/dl | 10-40 mg/dl         |
| CD4 Cells (% percentage)    | 6 (% percentage) | 30-61 (% percentage) |
| Absolute CD4 count          | 56 cells/ul | 490-1740 cells/ul   |
| Free Kappa Light Chain      | 351.8 mg/L | 3.3-19.4 mg/L        |
| Free Lambda Light Chain     | 167.5 mg/L | 5.7-26.3 mg/L        |
| Free Kappa/Lambda Ratio     | 2.10       | 0.26-1.65            |

| Serology                    | Value     | Reference Range      |
|-----------------------------|-----------|----------------------|
| Hepatitis Bs Antigen        | Positive  | Negative             |
| Hepatitis Be Antigen        | Positive  | Negative             |
| Hepatitis Be Antibody       | Negative  | Negative             |
| HIV RNA copies/ml Ultra     | 39400     | 20-10,000,000 copies/ml |
| HIV-1 RNA (PCR) log 10      | 4.595     | Log10 copy/ml        |

**TABLE 1: Laboratory Work**
Renal ultrasound showed increased parenchymal echogenicity in both kidneys followed by a right renal biopsy that revealed FSGS with collapsing features, acute tubular injury, and mild to moderate interstitial fibrosis. There were 17 glomeruli, two of which were completely sclerotic with findings of focal and mild mesangial hypercellularity. Up to five glomeruli had features of focal segmental glomerulosclerosis, including bowman’s capsular adhesions, segmentally solidified capillary lumina, and urinary space collagen (Figure 1). In addition, there was mild to moderate mononuclear cell inflammation noted in the interstitium with non-atrophic tubules showing features of injury such as apical cytoplasmic blebbing, broken brush borders, and tubular cell mitotic figures (Figure 2).

![Renal Biopsy](image)

**FIGURE 1: Renal Biopsy**

Renal biopsy histology demonstrated segmental sclerosis with crescentic features indicative of focal segmental glomerulosclerosis.
FIGURE 2: Renal Biopsy

Renal biopsy histology demonstrated denudation of renal tubular cells and loss of brush borders. Immunofluorescence microscopy consisted of mesangial regions and capillary walls staining mostly for IgA and IgM. Three out of 11 glomeruli were completely sclerotic with mesangial regions and capillary walls staining for IgA (1+), IgM (5+), C5 (trace), kappa (trace to 1+), and lambda (trace to 1+) in a granular pattern (Figure 3). Tubular epithelial cell protein reabsorption droplets were stained for albumin (3+), kappa (1 to 2+), and lambda (1 to 2+).
FIGURE 3: Immunofluorescence Microscopy

Immunofluorescence microscopy demonstrated mesangial regions stained for IgA (1+), IgM (3+), C3 (trace), kappa (trace to 1+), and lambda (trace to 1+) in a granular pattern.

Electron microscopy demonstrated extensive effacement of podocyte foot processes. Electron dense deposits were located in mesangial regions with few in the subendothelial, subepithelial, and intramembranous regions (Figure 4). Glomerular basement membrane had the normal trilaminar structure with moderate thickening.
FIGURE 4: Electron Microscopy
Electron microscopy demonstrated effacement of podocyte foot processes with electron dense deposits in the mesangial, subendothelial, subepithelial and intramembranous regions.

The patient was observed to have HIVAN and FSGS with collapsing features, HIVICK, and ATN. He improved symptomatically throughout his hospitalization, was discharged on highly active antiretroviral therapy (HAART) with prophylactic antibiotics, and was recommended to follow up very closely with nephrology and infectious disease specialists.

Discussion
HIVAN is a distinct clinicopathologic syndrome predominantly involving African American patients. Susceptibility to genetic mutations of APOL1 in patients of African descent is associated with the development of FSGS [4]. As per the literature, patients with HIVAN are mostly black with CD4 <200/mL (P = 0.01) and glomerular filtration rate <30 mL/min/1.73m² (P < 0.01) [5]. HIVAN’s overall prevalence varies according to the population’s demographic features with ~10% to 15% of HIV-infected patients developing HIVAN [1].

HIVAN can occur at any stage of the HIV infection, although most patients show significant immunosuppression and advanced infection at the time of the diagnosis. Its histopathologic features are represented in about 80% of cases by focal segmental glomerulosclerosis with collapse of the glomerular tuft in some glomeruli without prominent mesangial expansion or basement membrane thickening, extensive tubular ectasia, and tubulointerstitial changes [1].

The occurrence of hepatitis B, being a well-known cause of membranous nephropathy (MN), has also been reported in FSGS [6]. There have been previous cases, seven reported, two of which demonstrated hepatitis B surface antigen in the renal tissue and a response to lamivudine, indicating a possible causal association between the viral infection and occurrence of nephrotic syndrome [7]. As to the patient’s cocaine use disorder, it is likely the contributing etiology of his ATN [8]. Also, his panel depicts a polyclonal gammopathy that is not uncommonly reported in patients with HIV infection. Polyclonal hypergammaglobulinemia in turn promotes the development of circulating immune complexes, their passive trapping, or the in situ deposition of the antibodies binding to HIV viral antigens [9].
In terms of pathogenesis, HIV nucleic acid in podocytes, parietal epithelial cells, tubular epithelial cells, T-cells, and macrophages in human HIVAN renal biopsy specimens support the presence of the HIV gene. The kidney acts as a compartment separate from the blood where HIV-1 can replicate even in patients with serological remission [10].

Clinically, the classic presentation of HIVAN includes rapidly progressive renal failure, moderate to nephrotic range proteinuria, bland urinary sediment, and ultrasound findings of large, highly echogenic kidneys [11]. Studies regarding the optimal treatment of HIVAN with HAART patients involve initiation of HAART, steroids, and angiotensin-converting enzyme inhibitors [12]. In multivariate analysis, HIVAN risk was reduced by 60% (95% CI, 30 to 80%) by use of HAART, and no patient developed HIVAN when HAART had been initiated prior to the development of AIDS [13]. Also, the pathogenic role of HIV replication in the development of HIVICK for patients on HAART reveals improvement of kidney function by renal biopsy. Although therapies for this condition have produced contradicting results, HAART may prolong nephropathic patient survival. Keen follow-up of proteinuria and kidney function remains vital.

Conclusions
This case highlights that HIV-positive patients are at an increased risk of developing complex focal glomerular, immune, and tubular kidney pathologies, especially in the setting of acute infections, drugs, and non-compliance. HIVAN and HIVICK can coexist in some cases, mostly in the context of patients being off HAART with low CD4 counts and high viral loads. Hepatitis B could cause FSGS in a small percentage of patients, less likely in our patient’s case. Cocaine use disorder contributes to ATN. Nephrologists and infectious disease specialists should work together to screen a seropositive population with important infectious disease specialists should work together to screen a seropositive population with important proteineuria (>1 g/24 h) consistent with HIVAN and confirm the diagnosis by renal biopsy. Although therapies for this condition have produced contradicting results, HAART may prolong nephropathic patient survival. Keen follow-up of proteinuria and kidney function remains vital.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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