

## Research Article

# HIV Immune Complex Kidney Disease (HIVICK) Secondary to Syphilis Infection

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**Abstract**

The principal renal glomerular diseases described in HIV-infected patients are HIV associated Nephropathy (HIVAN) and HIV Immune Complex Kidney Disease (HIVICK). The highly active antiretroviral therapy (HAART) used in HIV infection led to a decrease in HIVAN incidence, but its effect on HIVICK incidence is not clear. We described two cases of HIVICK secondary to Syphilis presented as a rapidly progressive glomerulonephritis associated with diffuse proliferative glomerulonephritis (DPGN) in the renal biopsies. There are few cases in literature to date describing DPGN secondary to Syphilis. Since HIV became a chronic infection, safe sex is practiced less, the incidence of Syphilis infection is increasing and uncommon renal manifestations of Syphilis presented as a HIVICK in HIV infected patients must be expected.

**ABBREVIATIONS**

HIVAN: HIV associated Nephropathy, HIVICK: HIV Immune Complex Kidney Disease, HAART: highly active antiretroviral therapy, GN: glomerulonephritis DPGN: diffuse proliferative glomerulonephritis, HCV: hepatitis C.

**INTRODUCTION**

The principal renal disease described in HIV-infected patients was a focal and segmental glomerulosclerosis subsequently termed as 'HIVAN'. HIVAN is best characterized by nephrotic range proteinuria and azotemia with a rapid progression to terminal renal failure; normal-to-large kidneys on ultrasound scan, normal blood pressure, and collapsing Focal Segmental Glomerulosclerosis associated to microcystic tubulopathy on renal biopsy [1]. The prevalence of HIVAN has a significant geographical and ethnic diversity and has been reported higher in HIV-infected black patients [2].

The HIVAN was synonymous of renal disease in HIV-infected patients in the first two decades of the global pandemic. However, suppression of HIV replication and partial restoration of immune competence following administration of highly active antiretroviral therapy (HAART) has resulted in the prolongation of the survival of HIV infected individuals and in a significant decrease of HIVAN as a cause of renal disease mainly in areas of the world with adequate medical resources, where medical therapy was available to all persons and the patient is compromised with your therapy [3].

In HAART era has been observed more frequently the presence of the other more common kidney diseases in HIV infected people, such as the acute renal injury associated mostly to HAART nephrotoxicity and other secondary glomerular diseases, related to HIV coexisting conditions, such as diabetes, hypertension, and intravenous drug use [4,5]. However, the epidemiological behavior of HIVICK is not changing and recently published findings showed its increase among patients co-infected with HIV and hepatitis compared with those with HIV alone [6], that showed us the growth tendency of HIVICK secondary to sexually transmitted infections.

Although the racial predilection of, clinical risk factors for, pathologic characteristics of, and the HAART action for HIVAN have been well described [7], less is known about a large spectrum of pathologies ranging from postinfectious to "lupus-like" glomerulonephritis (GN), collectively referred to HIV Immune Complex Kidney Disease (HIVICK). Whether racial predilection exists for HIVICK it is not clear, however, it has been demonstrated higher HIV viremia associated with HIVICK on renal biopsy and that may suggest a pathogenic mechanism for the development of immune complex GN in HIV, either by disruption of normal immune function and regulation, or via direct antigenic stimulation and subsequent antibody response [8].

The UNAIDS report 2014 revealed that there is a slow decline in new HIV infections, mainly by the decrease of HIV infection in children. However, in some countries, with a large number of people living with HIV, new infections through sexual

transmission among young people increased, at least one third of new infections occur among young people aged 15–24 years and it demonstrated higher co-infection of these people with the viral hepatitis. Of the 35 million people living with HIV, hepatitis B is present in 2 for 4 million and hepatitis C in 4 for 5 million of them [9].

In the past, acquiring HIV meant certain death and nowadays a person on HIV treatment has nearly the same life expectancy as a person who does not have the virus. However, safe sex practice has been neglected and the increasing incidence of other sexually transmitted diseases such as viral hepatitis and Syphilis has been observed in these people and these diseases may be responsible for the emergence of HIVICK. The aim of this study is to report two HIVICK cases secondary to Syphilis infection as well as the prompt recovery of renal disease after the adequate antibiotic therapy beginning.

## CASES REPORT

### Case 1

A 19-year-old white male with history of malaise, fatigue and decreased urinary volume presented to the emergency department. Physical examination revealed pallor, legs oedema ++/4+ and, blood pressure of 150 X 90 mmHg. There were no other significant physical signs. Laboratory test showed were hemoglobin 9,8 g/dL, Hct 30.2%, WBC 4500, platelets 196 000/mm<sup>3</sup>, glucose 90 mg/dL, potassium 5.1 mEq/L, sodium 137 mEq/L, urea 104 mg/dL, creatinine 2.1 mg/dL urinary dipstick test Protein ++ and Hb +++. The diagnosis of Acute kidney Injury was made and he was transferred after to our hospital.

At hospital admission the blood pressure was 170 X 90 mmHg and legs oedema ++/4+. There was no relevant medical past history or drug abuse. Furosemide and Enalapril maleate were begun. In the fourth day after the admission he presented a disseminated cutaneous rash with a papular eruption involving the entire trunk and the extremities, including the soles of the feet. The dermatological consultation showed Syphilis as diagnosis.

The laboratory tests results were hemoglobin 10.0 g/dL, Hct 31.6%, WBC 4600, platelets 200 000/mm<sup>3</sup>, glucose 86 mg/dL, albumin 2.1 mg/dL, potassium 4.9 mEq/L, sodium 138 mEq/L, cholesterol 320 mg/dL, and triglycerides 280 mg/dL, urea 92 mg/dL, creatinine 3.0 mg/dL, creatinine clearance ( $C_{cr}$ ) = 27.2 ml/min, proteinuria ( $P_u$ ) = 3.6g/24h, beta 2 microglobulin 0, 32mg/24h and urinalysis showed aseptic leukocyturia, hematuria, hyaline and granular casts..

Serum complement was: C3: 92 mg/dL, C4:19 mg/dL. PCR RNA-HIV180.000 copies/ml, CD4 184 cells/mm<sup>3</sup> e CD8 de 633 cells/mm<sup>3</sup>. Anti-nuclear antibody, Coombs and serological evaluation for viral hepatitis C and B, Cytomegalovirus and Parvovirus were negative. The VDRL: 1/152 and FTA-Abs IgM were positive. Ultrasonography showed hyperecogenic normal size kidneys.

Renal biopsy was performed on the 4<sup>th</sup> day, obtained 12 glomeruli and demonstrated diffuse proliferative glomerulonephritis with the presence of cellular crescents in two (16, 6%) glomeruli and associated with interstitial inflammatory infiltrate and oedema. No vascular lesion was seen. Immunofluorescence microscopy showed only the presence of IgG and C3 granular in the mesangium.

### Case 2

A 32-year-old black homosexual male presented three weeks before his admission asthenia, anorexia and legs oedema associated to foamy urine and arterial hypertension. He was an HIV-infected patient diagnosed from 4 years that was receiving HAART with AZT, Lamivudina e Efavirens. Furosemide was begun and the laboratory tests showed creatinine 2.1 mg/dL and nephrotic proteinuria in urine spot. He was referred to our hospital for further nephrological evaluation. One month before of the onset of symptoms the laboratory tests were normal: creatinine 1.1 mg/dL, urea 32 mg/dL and normal urinalysis. There was no relevant medical past history or drug abuse.

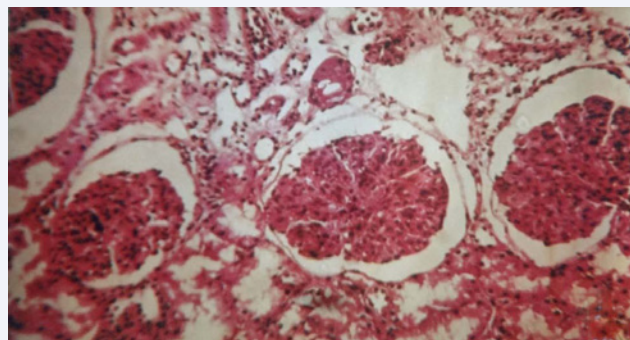
At hospital admission Physical examination revealed blood pressure of 140 X 70 mmHg, mild periorbital and legs oedema and ulcerated lesion in the oral cavity. There were no other physical signs. The laboratory tests results were hemoglobin 11.9 g/dL, Hct 37.6%, WBC 7000, platelets 156 000/mm<sup>3</sup>, erythrocyte sedimentation rate 56, glucose 86 mg/dL, albumin 2.4 mg/dL, potassium 4.6 mEq/L, sodium 138 mEq/L, cholesterol 260 mg/dL, and triglycerides 240 mg/dL, urea 92 mg/dL, creatinine 3.2 mg/dL,  $C_{cr}$  = 23,1 ml/min,  $P_u$  = 4.6g/24h, beta 2 microglobulin 0,21mg/24h and urinalysis showed aseptic leukocyturia, hematuria, hyaline and granular casts.

Serum complement was: C3: 96 mg/dL, C4:26 mg/dL. PCR RNA-HIV undetectable, CD4 624 cells/mm<sup>3</sup> e CD8 de 973 cells/mm<sup>3</sup>. Anti-nuclear antibody and serological evaluation for viral hepatitis C and B, Cytomegalovirus was negative. The VDRL: 1/128 and FTA-Abs IgM were positive. Ultrasonography showed hyperecogenic enlarged kidneys and small bilateral pleural effusion.

Renal biopsy (Figure 1) was performed on the 3<sup>rd</sup> day, obtained 15 glomeruli and demonstrated diffuse proliferative glomerulonephritis associated to the presence of cellular crescents in three (20%) glomeruli and focal interstitial inflammatory infiltrate and oedema. No vascular lesions were seen. Immunofluorescence microscopy showed only the presence of IgM and C3 granular in the mesangium and capillary loops.

### Differential diagnosis

Several etiologies for kidney disease in these two HIV infected patients were considered, including the following: NAHIV, NAVICK, nephrotoxicity secondary to HAART, other drugs'



**Figure 1** Three glomeruli with proliferation of mesangial and endothelial cells, lobular accentuation, partial occlusion of the capillary lumen and the presence interstitial oedema. (HE 20X).

nephrotoxicity, nephropathy secondary to neoplastic diseases associated to HIV infection. The diagnosis of rapidly progressive glomerulonephritis secondary to DPGN associated to Syphilis was done, based in clinical, laboratorial and histopathological data.

## Management

When the diagnosis of rapidly progressive glomerulonephritis secondary to Syphilis was considered, the treatment with benzathine penicillin G 2.400.000 UI / week / 3 weeks plus methylprednisolone pulse therapy 1g / day / 3 days were promptly started.

In first case the HAART was begun after Syphilis treatment and the patient was discharged home on the 28<sup>th</sup> hospital day with serum urea 42 mg/dL, creatinine 1.1 mg/dL  $C_{cr} = 88,7$  ml/min  $P_u = 480$ mg/24h and in the second case the patient was discharged home on the 12<sup>th</sup> hospital day with serum urea 46 mg/dL, creatinine 1.6 mg/dL, he was seen in the outpatient clinic thirty days after the discharge and was asymptomatic with serum urea 42 mg/dL, creatinine 1.0 mg/dL,  $C_{cr} = 86,3$  ml/min and  $P_u = 600$  mg/24h.

## DISCUSSION

Syphilis is caused by *Treponema pallidum* and is considered the 3<sup>rd</sup> most common sexually transmitted disease among adults, after gonorrhea and lymphogranuloma venereum. It can be transmitted by sexual contact (the most common form of transmission), congenitally via the placenta, or as a result of an infected blood transfusion or accidental inoculation. In developed countries, largely due to the discovery of penicillin, syphilis was practically wiped out in the 1950s, however, in recent years we have been witnessing a resurgence of this disease and the new cases occur predominantly in young homosexual men and a large proportion of them present co-infection with HIV [10].

There is a higher prevalence of syphilis among vulnerable populations, which includes sex workers associated to unsafe sexual practices and involvement with illicit drugs, but we also have observed a high prevalence among HIV-infected patients [11]. WHO estimates 12 million new cases of syphilis worldwide and the greatest burden is in adolescents and young adults and it has been demonstrated that HIV and syphilis co-facilitate transmission of each other and behaviors that are risky for transmission of syphilis are also risky for transmission of HIV [12].

It is usually expressed after an incubation period of 12 to 30 days, the emergence of ulcer or chancre syphilitic skin, mucous membranes of the airways and digestive tract and / or genitals corresponding to the input port of the causative agent and may be associated with fever and lymphadenopathy. We can observe the evolution to the disseminated form, by dissemination via the blood or lymph, with parenchymal lesions, and the onset of secondary glomerulonephritis may occur. The diagnosis of syphilis is made by serological tests for the detection of antibodies nontreponemal (VDRL reaction) and testing for treponemal antibodies, which are indicated as confirmatory tests and can be performed by indirect immunofluorescence (Fluorescent Treponemal Antibody Absorbed Test - FTA-Abs) and only becomes positive after 3 weeks of infection [13].

Nephropathy is an uncommon complication, but well known

in syphilis, with higher frequency in the past, during the pre-antibiotic era, when it was described. The prevalence was 0,3 to 0,4% in large series [14] and can cause a wide variety of clinical and pathological forms of renal disease, as immune complex-mediated glomerulonephritis (GN): membranous GN, mesangial GN, rapidly progressive GN, diffuse endocapillary GN with or without extracapillary formation or minimal change GN have been described [15].

Proteinuria is the most common clinical manifestation. Although the association between syphilis and renal disease had been known for over 100 years, there are few cases reported in literature in review on the subject, which makes diagnosis more difficult, as it is seldom suspected in clinical practice. However, Syphilis must be considered in the differential diagnosis in children and all sexually active adults with nephritic or nephrotic syndrome [16], especially when associated with evidence of systemic infection or in HIV- infected individuals [17].

Similarly, the recent increment in syphilis incidence mainly in HIV-infected individuals, may foreshadow an incoming increase in all forms of syphilitic renal involvement from mild transient proteinuria to frank nephrosis associated with diffuse proliferative glomerulonephritis or rapidly progressive crescentic glomerulonephritis [18,19]. It has been described the action of *Treponema pallidum* as the cause of renal injury, including the development of proteinuria and glomerular injury during hematogenous dissemination of spirochetes. Antitreponema antibody has been eluted from renal glomerular deposits obtained by biopsy [20].

We report two cases of HIVICK secondary to Syphilis, where renal biopsies showed the presence of diffuse proliferative glomerulonephritis associated with crescents, benzathine penicillin G plus methylprednisolone pulse therapy were promptly administrated, and resolution of glomerular proteinuria and renal function supports syphilis as the cause of renal disease. Complete resolution of renal manifestations after antisyphilitic therapy is the rule in patients with syphilitic nephrotic or nephritic syndrome, regardless of the presence of HIV infection or of corticosteroids administration [16,17]

HAART consisting of at least three drugs active against HIV infection has revolutionized the management of HIV-AIDS and led to a change in the epidemiology of renal diseases in these patients, reducing drastically the incidence of HIVAN. HIVAN remains strongly associated with severe renal failure, black origin and CD4 lower than 200/mL at presentation, mostly in untreated patients or in those that have abandoned the treatment and, more recently, the genetic predisposition has been well described with the identification of a genetic susceptibility locus for the development of HIVAN in African Americans (MYH9/APOL1) (21). HIVAN almost exclusively affects patients of african american or west african descendent, as result of this genetic predisposition [22]. It has been recommended that the diagnosis of HIVAN is an indication for the initiation of anti-retroviral therapy regardless of CD4+ cell count [23].

Moreover, with the widespread use of HAART in the treatment of HIV infection a high incidence of renal diseases has been described, mainly acute kidney injury secondary to its nephrotoxic effects. Drug toxicity accounted for nearly 80% of tubulopathy cases. Tubular toxicity was usually observed



with a nucleotide analog reverse transcription inhibitor and the Tenofovir accounts for the main cause of tubulopathy [24]. Tenofovir is widely use as first line treatment of HIV infection and undergoes renal clearance by a combination of glomerular filtration and active tubular secretion. Patients receiving tenofovir must be monitored closely for early signs of tubulopathy (i.e., glycosuria, acidosis, mild increase in plasma creatinine levels, and proteinuria), even several months after the initiation of treatment; if there is any sign of tubulopathy, therapy should be stopped as soon as possible to avoid the risk of definitive renal failure [25].

HAART has provided better treatment options for HIV infection and is making this a chronic instead of fatal infection and the HIVAN incidence was drastically decreased, however, its beneficial effect on HIVICK is not established and the incidence was not changed on last years. As a consequence of HAART, HIV has become a chronic disease, safe sex is practiced less and the incidence of syphilis is rising rapidly nowadays among young people. Therefore, we can expect an increase of HIVICK number secondary to syphilis in these individuals. The syphilis diagnosis must always be thought in HIV infected patients with glomerular renal disease, since the renal lesion of syphilis may be severe, but is highly curable with opportune beginning of appropriate antibiotic therapy.

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