Kidney Disease in Human Immunodeficiency Virus-seropositive Patients: Absence of Human Immunodeficiency Virus-associated Nephropathy was a Characteristic Feature

Abstract

Human immunodeficiency virus (HIV) infection can cause a broad spectrum of renal diseases. However, there is paucity of Indian data on the patterns of renal lesions in HIV-seropositive patients. The aim of the present study was to delineate the spectrum of renal lesions in HIV/acquired immunodeficiency syndrome patients. In this prospective study, all HIV-positive patients of both genders aged >18 years were screened for renal disease. Patients with proteinuria of more than 1 g/24 h were subjected to renal biopsy. A total of 293 HIV-positive patients were screened; of these, 136 (46.4%) patients found to have renal involvement. Dipstick-positive proteinuria of 1+ or more was observed in 112 (38.2%) patients, and 16 (14.2%) patients had proteinuria of more than 1 g/24 h. Renal biopsy in 14 cases revealed glomerulonephritis (GN) in 12 (85.7%) (isolated GN in 4 [28.5%] and GN mixed with chronic TIN in 8 [57.1%]) patients. These include mesangioproliferative GN in 5 (35.7%), membranoproliferative GN in 2 (14.2%), focal segmental glomerulosclerosis in 2 (14.2%), diffuse proliferative GN in 2 (14.2%), and diabetic nephropathy in 1 (7.1%) patients. Chronic interstitial nephritis was noted in 10 (71.42%) (superimposed on GN in 8 [57.1%), isolated in 2 [14.2%]) patients. Granulomatous interstitial nephritis was seen in 3 (24.1%) cases. GN and chronic interstitial nephritis were noted in 85.7% and 71.42% of patients, respectively, mostly superimposed on each other. Mesangioproliferative GN was the most common glomerular lesion, but classical HIV-associated nephropathy was not observed.

Keywords: HIV-associated nephropathy, HIV infection, nephropathies, proteinuria

Introduction

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Renal disease is a relatively common complication in patients with HIV infection globally, and prevalence of renal disease in HIV patients is about 5–30%. The spectrum of renal diseases, other than HIV-associated kidney disease, has changed and continued to vary across geographical regions worldwide. There is paucity of data on histological lesions of kidney in HIV patients from our country. The aim of our study was to analyze the spectrum of histological lesions in proteinuric HIV patients.

Materials and Methods

The study included HIV-seropositive patients of 18 years or above attending antiretroviral treatment (ART) center of our institute between August 1, 2010, and July 31, 2013. The National AIDS Control Organization (NACO) 2007 guideline was used for the diagnosis of AIDS and HIV infection in our study. All patients included the introduction of cART, whereas incidence of non HIV-associated chronic kidney diseases (CKD) has increased in post-cART era. The distribution of HIV-associated kidney disease has changed and continued to vary across geographical regions worldwide. There is paucity of data on histological lesions of kidney in HIV patients from our country. The aim of our study was to analyze the spectrum of histological lesions in proteinuric HIV patients.
in the study were screened for evidence of clinical renal disease using urinalysis, serum creatinine estimation, and ultrasound scan of the kidneys. HIV-positive patients of both genders with clinical renal disease, were subjected to detailed history, physical examination, laboratory investigation including complete blood picture, urine analysis, renal function test, liver function test, random blood glucose, CD4 count, ultrasound of the abdomen, ECG, and chest X-ray PA view. The urine was tested using dipstick method for detection of proteinuria. Those patients having a dipstick proteinuria of 1+ or more were subjected to quantitative 24-h urinary protein estimation. Percutaneous ultrasound-guided kidney biopsy was done in patients with proteinuria of ≥1 g/24 h. Criteria for kidney biopsy were: (1) HIV seropositive, (2) proteinuria of ≥1 g/day, and (3) patients not taking combined antiretroviral therapy (cART) before study. Biopsy was not done in the presence of contraindication or refusal to the procedure. The HIV-positive patients with CD4 lymphocytes count <350 cells/mm³, and all patients with HIV-associated kidney disease regardless of CD4 lymphocytes count were prescribed highly active antiretroviral therapy (HAART).

The kidney tissue was studied under light microscopy, using hematoxylin and eosin, periodic acid–Schiff, acid fuchsin orange green, and silver stains (for fungus). Electron microscopy and immunofluorescence staining were not done due to lack of facility at our center. Based on standard morphology of the kidney tissue on histological observation, the various spectrums (glomerular and tubular) of kidney lesion were studied in proteinuric seropositive HIV patients.

Results

Two hundred and ninety-three (male 176; female 117) HIV-positive patients were recruited in the study. Of 293 patients, 201 had clinical AIDS and 92 cases were HIV positive. The clinical renal disease was noted in 136/293 (46.4%) cases. Dipstick proteinuria of 1+ or more was observed in 112 (38.2%) of patients. Sixteen (14.2%) patients had proteinuria of more than 1 g/24 h. These 16 HIV-positive cases (Male 11 and female 5) were considered for renal biopsy. Kidney biopsy was not done in two cases because of bilateral contracted kidneys [Figure 1]. Thus, renal biopsy was done in 14 patients. Baseline clinical characteristics of HIV patients are shown in Table 1.

Renal histology

Of 16 HIV-seropositive patients with proteinuria of ≥1 g/24 h; biopsy was done in 14 and 2 cases were excluded from the study because of bilateral small kidneys. The spectrum of renal histological features in 14 patients is shown in Table 2. We noted overall glomerulonephritis (GN) in 12 (isolated 4, mixed lesion: GN combined with interstitial nephritis 8) and chronic interstitial nephritis in 10 (isolated 2; superimposed on GN 8) patients. The most common glomerular lesion was mesangio proliferative GN (n = 5; 31.25%). Focal segmental glomerulosclerosis (FSGS), mesangiocapillary GN, and diffuse proliferative GN were noted in two cases each (n = 2; 12.5%). Diffuse diabetic glomerulosclerosis was noted in one HIV-positive diabetic patient. Chronic tubulointerstitial lesions were seen in 10 (isolated 2; in association with glomerular 8) cases. Granulomatous interstitial nephritis was noted in three cases in association with glomerular diseases. Focal proliferative GN with crescent and focal GBM thickening was observed in one patient. We did not observe classical lesion of HIVAN in our study.
AIDS due to HIV infection was first recognized in the United States in 1981. HIV-related renal diseases include various histological spectrum that consists of HIVAN, HIVICK, thrombotic microangiopathy, cART-related nephropathies, and comorbidities-associated nephropathies in HIV patients (such as HCV infection, hypertension, and diabetes). AIDS-associated nephropathy – known as HIVAN – was first reported in the United States in 1984. HIVAN results from direct viral interaction of renal cells or the action of viral proteins. The characteristic pathological lesion in HIVAN is collapsing FSGS, microcystic tubular dilatation, and endothelial tubuloreticular inclusion on ultrastructural examination. Mean age of our study population was 35.7 ± 9 years with male and female distribution of 176 and 117, respectively. The higher number of males may be a reflection of higher mobility of this age group in search of livelihood, high sexual activity phase, and to some extent highly emotional and stressful life which usually prevails at this age and sex group. Our finding was in accordance with those from the US and Brazil.

Prevalence of dipstick-positive proteinuria among the HIV-seropositive patients is highly variable in different studies and in different geographical regions. In our study, the prevalence of dipstick proteinuria was 38.2%. Proteinuria was reported in 29.8% and 14% of patients, respectively, in two studies from the USA. Proteinuria ranged between 6% and 32% in various studies from the USA and Europe. Reported prevalence of proteinuria in HIV patients was much lower (5–6%) in studies from Africa, Brazil, and Ethiopia. Range of proteinuria was 17.6%–28% from various Indian studies.
proteinuria was noted in 38.2% of cases, and ten patients had active urinary sediments in the present study. Thus, high prevalence of proteinuria in our patients was comparable to other studies. The higher degree of proteinuria is possibly related to delay in diagnosis, lack of awareness, low education level, and social stigma attached to HIV infection in our study.

HIVAN has been consistently reported to be the most common glomerular lesion in HIV-seropositive patients from the US, Brazil, African countries, and Western Europe. Classic HIVAN histopathology can be seen in adults and children at any stage of HIV infection but is most common in the advanced diseases, including AIDS. West African descent is highly susceptible to classical HIVAN. HIVAN has been reported from other Asian renal biopsy studies. In a series of 26 biopsies in HIV-infected patients in the Indian cohort, however, the disease is notably absent in Swiss–European and Thai population. The current prevalence of HIVAN is declining as result of the widespread use of cART. Without cART, HIVAN progresses rapidly to end-stage renal disease (ESRD). HIVAN was noted in 34% of patients in Chicago. A study from South Africa reported HIVAN in 33% of cases. We have not observed evidence of HIVAN in HIV-infected patients in the present study. In two (14.2%) cases, biopsy evidence of collapsing FSGS was seen, but classical features of HIVAN were absent. In a northern Italian study from three hospitals, no case of FSGS had been found in a large Caucasian cohort. Other studies from Ethiopia and Thailand also could not find any case of HIVAN. Varma et al. from India did not find any case of HIVAN but reported one case of collapsing FSGS and four cases of noncollapsing FSGS. The first case of classical HIVAN was reported from India in the state of Jammu and Kashmir. Two cases of HIVAN were reported from South India among HIV-infected children presented with nephrotic-range proteinuria. In 2013, Gupta et al. reported collapsing FSGS in 2 of 26 patients, but classical HIVAN was not seen. Even though HIVAN is a rare entity, collapsing FSGS is not uncommon in this part of the world.

The most common glomerular lesion was mesangioproliferative GN noted in 5/14 (35.7%) patients. In contrast to our study, mesangioproliferative GN has been reported infrequently from the Western world. No case of mesangioproliferative GN has been reported in the major biopsy series from the United States. Mesangioproliferative GN was reported in 4/26 (15%) of patients from Italy. A study from South Africa revealed mesangioproliferative GN in 6% of HIV patients. However, a high incidence of mesangioproliferative GN has been reported from other Asian renal biopsy studies. In a series of 26 biopsies in HIV-infected patients in Thailand, mesangioproliferative GN was observed in 65% of the cases. In a study from India, with 25 patients, 8 cases (32%) had mesangioproliferative GN. Similarly, Gupta et al. reported mesangioproliferative GN in 10/26 patients (38.4%) as the most common glomerular lesion. Thus, mesangioproliferative GN is an inconsistent finding in the American, African, and European studies. However, it represents a dominant renal lesion in HIV-infected individuals in Asia. HIV-associated lupus like GN and thrombotic microangiopathy were not observed in our study.

Epidemiological data showing a decline in the incidence of HIVAN and HIV-associated ESRD in the United States after introduction of cART, suggest that effective control of viral...
replication can prevent the development of HIVAN.[40,41] A study of 221 HIV-positive patients in South Africa reported that both HIVAN and HIVICK showed response to cART.[42] HIV-associated thrombotic microangiopathy also appears to benefit from ART, and a decline in incidence has been reported with widespread ART use.[43] Thus, combined ART has changed the epidemiology of HIV-related kidney diseases. HIVICK and noncollapsing form of FSGS are increasingly reported in the post-cART era.[44] HIVICK is less likely than HIVAN to progress to ESRD and thought to be associated with greater exposure to cART and hepatitis C coinfection.[45] Over the past two decades, a decreasing frequency of classic HIVAN has been observed in African patients living in Europe.[46] cART has been associated with lower incidence of HIVAN, improved kidney function, and lower risk of ESRD in observational studies of patients with biopsy-confirmed or clinically suspected HIVAN. These data reveal that cART seems to have a beneficial role in the prevention and treatment of HIVAN.[44] The HIV Medicine Association of the Infectious Disease Society of America recommended that all patients with HIV-associated kidney disease should receive ART.[47]

Isolated chronic interstitial nephritis was the predominant nonglomerular lesion in our study (15.38%). We observed chronic tubulointerstitial nephritis in association with glomerular lesions in six cases (46%). The granulomatous interstitial nephritis was observed in 23% of patients in association with other glomerular lesions. One of them was secondary to tubercular infection; the etiology of others was unknown. Unlike mesangio proliferative GN, tubulointerstitial diseases have been consistently reported in other studies, but the incidence was low in most of the studies.[16,37,38] However, a high incidence of interstitial nephritis was reported in a multicentric study from Paris; 48% (14/29) in African Americans and 52% (16/31) of Caucasian patients had interstitial nephritis in their series of sixty patients.[48] The prevalence of interstitial nephritis was 20% in another study from India.[21]

**Conclusion**

The prevalence of dipstick-positive proteinuria in our HIV-seropositive patients was high (38%) and bears no relation to duration of HIV, CD4 count, HAART therapy, and serum creatinine levels. Chronic interstitial nephritis, either in isolation or superimposed on other glomerular lesion, was very common (71%). Mesangio proliferative GN was the most common glomerular lesion similar to other Indian studies. The absence of HIVAN in our HIV patients with proteinuria was a characteristic feature.

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**Conflicts of interest**

There are no conflicts of interest.

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