Fibrillary glomerulonephritis in a human immunodeficiency virus-positive, hepatitis C-negative Indian patient: Expanding the profile of renal involvement in human immunodeficiency virus infection

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ABSTRACT

Highly active anti retroviral therapy (HAART) has dramatically improved life expectancy of human immunodeficiency virus (HIV) infected patients, converting HIV infection into a chronic illness with associated changes in its attendant renal complications. The past two decades have witnessed a decrease in the prevalence of HIV associated nephropathy (HIVAN), traditionally considered to be the hallmark of renal involvement in HIV infection. Simultaneously a host of other glomerular and tubulo-interstitial diseases have emerged, expanding the spectrum of HIV associated renal diseases, predominant among which is HIV associated immune complex mediated kidney diseases (HIVICK). Of the diverse glomerular diseases constituting HIVICK, fibrillary glomerulonephritis (FGN) remains a rarity, with only two existing reports to date, confined to patients co-infected with Hepatitis C virus (HCV). The pathogenetic role of HIV in these patients remains under a cloud because of previously well established association of HCV infection and FGN. We report a case of FGN in a HIV seropositive, HCV negative patient, highlighting the diagnostic electron microscopy (EM) findings of FGN and strengthening the causal association of HIV with FGN. In view of increasing heterogeneity of renal complications in HIV infection, the diagnostic utility of a comprehensive renal biopsy evaluation inclusive of EM is emphasized for appropriate selection of treatment modalities.

KEY WORDS: Fibrillary glomerulonephritis, HIV associated immune complex mediated kidney disease, HIV associated nephropathy, HIV associated renal disease, Human Immunodeficiency virus infection

INTRODUCTION

With the advent of highly active antiretroviral therapy (HAART), the disease burden of renal involvement in human immunodeficiency virus (HIV)-infected patients is currently on the rise along with a parallel change in its profile. A wide spectrum of HIV-associated immune complex-mediated kidney disease (HIVICK) has been described of late, especially in Caucasian and Asian populations,[1,2] in addition to classical HIV-associated nephropathy (HIVAN). HIVICK lesions with organized glomerular deposits are quite rare and mostly described in patients with concurrent seropositivity for hepatitis C virus (HCV).[3,4] The causative role of HIV in such scenarios remains suspect. We report a case of fibrillary glomerulonephritis (FGN) in an HIV-positive but HCV-negative patient, emphasizing the role of renal biopsy with ultrastructural analysis in the diagnosis and management of HIV-infected patients with renal disease.
CASE REPORT

A 46-year-old Indian male presented with bilateral pedal edema and weakness of 6-month duration. He gave a past history of being diagnosed with HIV infection, 9 years back, but had never taken HAART, opting for native/nonallopathic medical treatment at the time. He was not on follow-up till 2 months before current presentation when he developed pyrexia of unknown origin, weight loss, and anorexia for which he was initiated empirically on antituberculous treatment (ATT) with isoniazid, rifampicin, pyrazinamide, and ethambutol at his local medical center. However, ATT was discontinued after 5 days when he developed vomiting and was found to have transaminitis. He was referred to us for further management, on suspicion of ATT-induced hepatitis and background history of positive retroviral status.

Physical examination was remarkable for oral candidiasis, bilateral pitting pedal edema, right supraclavicular lymph node enlargement, bilateral pleural effusion, and nontender hepatomegaly extending 4 cm below the right costal margin. There were no lymph node swellings elsewhere. Blood pressure was 140/80 mmHg. Laboratory studies showed serum creatinine – 1.67 mg/dL and 24-h urinary protein – 3.2 g; urine analysis showed 23 red blood cells and 2–3 white blood cells per high-power field. Complement levels were normal (serum C3: 104 mg/dL [normal 90–180] and serum C4: 10.9 mg/dL [normal 10–40]). Hepatitis B surface antigen, hepatitis C antibody, and polymerase chain reaction were negative, and there were no detectable cryoglobulins or monoclonal bands. CD4 count was 119 cells/μL and liver function tests were normal apart from serum albumin of 2.1 g/dL. HIV serology was positive for HIV-1 antibodies. Pleural fluid aspirate showed a lymphocyte predominant transudative effusion. Biopsy of the right supraclavicular lymph node revealed caseating granulomatous inflammation, with culture growing Mycobacterium tuberculosis. Chest X-ray and ultrasound abdomen did not show any hilar or abdominal lymph node enlargement.

With a working clinical diagnosis of HIVAN, an ultrasound-guided percutaneous renal biopsy was performed to ascertain the cause of nephrotic-range proteinuria.

Light microscopic examination of renal tissue cores received, showed a total of 19 glomeruli with 12 glomeruli on 4 micron thin (H&E stained) sections and 7 glomeruli on 1 micron semi-thin (toluidine blue stained) sections respectively. There was diffuse mesangial expansion and focal mesangial hypercellularity associated with irregular capillary wall thickening. Five glomeruli were globally sclerosed and two showed secondary focal segmental sclerosis. Focal double contouring of capillary walls with segmental endocapillary proliferation was noted. The interstitium showed foci of fibrosis with tubular atrophy (IFTA) involving up to 25% of the cortical tissue present in the core examined. Few dilated tubules containing hyaline casts and aggregates of chronic inflammatory cells were seen adjacent to these foci. Hyaline arteriosclerosis and arteriolar sclerosis were observed [Figure 1a-c]. There were no collapsing features or podocyte hyperplasia to suggest HIVAN. Features of acute tubular injury were not present. Immunofluorescence showed granular peripheral capillary wall deposits of immunoglobulin G (IgG) (2+), IgM (2+), IgA (1+), and C3 (1+). There was no light chain restriction. Congo red stain for amyloid was negative [Figure 1d]. Based on these findings, a preliminary diagnosis of HIV-associated immune-mediated proliferative glomerulonephritis was made.

Electron microscopy demonstrated expansion of the mesangium by fibrillary deposits extending into the capillary walls and focally involving entire thickness of glomerular basement membranes. The deposits were composed of randomly oriented fibrils measuring 21–29 nm in diameter without central lucencies on cross section. Extensive foot process effacement was noted [Figure 2a-d]. There was no evidence of a microtubular substructure, ruling out immunotactoid glomerulonephritis (ITGN) and cryoglobulinemic glomerulonephritis. The final diagnosis was FGN with secondary focal segmental sclerosis in a case of HIVICK.

ATT was restarted and liver function remained normal. One month later, he was started on HAART with abacavir, lamivudine, and efavirenz. Proteinuria was managed with losartan. At last follow-up, proteinuria was 2 g/day and serum creatinine was 0.9 mg/dL.

DISCUSSION

The most common kidney lesion traditionally described in HIV-infected patients has been termed HIVAN presenting with FGN.
While HIVAN still remains the most common glomerulonephritis, cryoglobulinemic glomerulonephritis, ITGN, and FGN.[1,2] ITGN and FGN are uncommon glomerular diseases with immune deposits demonstrating organized substructure distinct from amyloid and cryoglobulins.[3] The association between ITGN/FGN and HCV infection is well recorded.[4] Only two cases of FGN associated with HIV infection have been reported to date, both of whom were coinfected with HCV.[5] rendering the pathogenic relationship to HIV unclear. Due to the heterogeneity of HIVICK lesions, contemporary renal research focuses on establishing causality and thereby optimizes immunosuppressive therapy of HIVICK in the already immunocompromised HIV-positive patient.[1] The present case of FGN occurring in a patient with HIV monoinfection whose renal symptoms responded to treatment for HIV infection is a valuable pointer to the causal role of HIV in this setting and also reinforces the value of HAART in managing HIVICK without additional cytotoxic therapies for immunosuppression.

Passive trapping of circulating immune complexes resulting from polyclonal hypergammaglobulinemia in HIV infection is the favored theory of pathogenesis of HIVICK and supported by the elegant demonstration of HIV antigens p24, gp41, and gp120 bound to IgG or IgA antibodies in circulating and tissue immune complexes in HIV-infected patients.[2] It is possible to speculate further on the physiochemical nature of the fibrillary deposits by analogous comparison to HCV-related FGN in which a “slow cryoglobulin” (not detectable by standard tests for cryoglobulins) with affinity for matrix proteins such as fibronectin has been postulated to form organized fibrils.[6]

This case illustrates the need to lower our threshold for performing renal biopsies in HIV-positive patients, in support of the “test and treat” policy advocated currently for HIV prevention and management.[1] A composite renal biopsy evaluation inclusive of ultrastructural analysis will go a long way toward expanding our knowledge on the epidemiology, pathogenesis, and optimal management of renal involvement in HIV.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
Matthai, et al.: Fibrillary glomerulonephritis in HIV infection
