HIV-Associated Nephropathy:

A Brief Review

TING-CHI LU, M.D., AND MICHAEL ROSS, M.D.

Abstract

HIV-associated nephropathy (HIVAN) is an important cause of renal failure in HIV-1 seropositive patients. The disease is characterized by collapsing focal segmental glomerulosclerosis with marked podocyte proliferation, microcystic dilatation of the tubules and interstitial nephritis. Patients generally present with advanced HIV-1 infection, renal insufficiency and marked proteinuria. No serologic markers exist to diagnose HIVAN, and given the broad differential diagnosis for renal failure in these patients, renal biopsy should be performed. Viral infection of renal cells plays a central role in the pathogenesis of HIVAN. There is now compelling evidence that highly active antiretroviral therapy (HAART) is effective in preventing end-stage renal disease in patients affected with HIVAN. The efficacy of angiotensin-converting enzyme (ACE) inhibitors and prednisone has also been evaluated, but larger prospective studies are needed.
Key Words: Nephropathy, glomerulosclerosis, nephritis.

Introduction

HIV-ASSOCIATED NEPHROPATHY (HIVAN) is a renal syndrome in HIV-1 seropositive patients, characterized by heavy proteinuria, renal dysfunction and rapid progression to renal failure. It was initially described in 1984 by Rao et al., who reported a pattern of sclerosing glomerulopathy in HIV-1 seropositive patients in New York City (1). It is now the third leading cause of end-stage renal disease (ESRD) in African Americans between the ages of 20 and 64 and the most common cause of ESRD in HIV-1 seropositive patients (2).

Patient Population

HIVAN is usually a late manifestation of HIV-1 infection; however, it has been reported to be the initial presentation of HIV-1 infection (3). Winston et al. evaluated 10 patients with biopsy-proven HIVAN. Although 50% of the patients were asymptomatic and had not suffered from opportunistic infections at the time of diagnosis, all had CD4 cell counts of less than 200 cells/mm^3. Furthermore, after reviewing prior studies of HIVAN in which CD4 cell counts were available, the authors found that of a total of 114 patients reported, only 6 did not have a CD4 cell count below 200 cells/mm^3 (480 – 1700 cells/mm^3) (4).

HIVAN is especially prevalent among patients of African descent (1, 5, 6). In the US, blacks are 12.2 times more likely to develop HIVAN than non-black patients (7). In the largest reported series from Europe, 97 of 102 patients with HIVAN were black (8).

Clinical Presentation

Patients typically present with renal insufficiency accompanied by proteinuria that is usually in the nephrotic range (9). In a study of 26 patients with HIV-1 associated nephropathy, the mean 24-hour protein excretion rate was 6.6 grams per day, with a mean serum creatinine concentration of 5.4 mg/dL (10). Despite the presence of heavy pro-

Department of Nephrology, Mount Sinai Medical Center, New York, NY.

Address all correspondence to Ting-chi Lu, M.D., Mount Sinai Hospital, Department of Nephrology, Box 1243, One East 100th Street, New York, NY 10029.

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teinuria, peripheral edema is uncommon. Hypertension is also surprisingly rare in most patients with HIVAN, leading some to speculate that HIVAN is a salt-wasting disease (8).

There are no specific serologic or urinary markers for HIVAN. Co-infection with hepatitis B and C is common and should be considered in all patients suspected to have HIVAN, because they are associated with membranous nephropathy and membranoproliferative glomerulonephritis, respectively. Renal ultrasound generally shows echogenic kidneys that are normal-to-large in size (11, 12).

In the evaluation of an HIV-1 positive patient, the first step is to rule out acute and reversible causes of renal failure. The differential diagnosis of renal failure is similar to that in non-HIV-1-infected patients. Complications of their underlying illness such as poor oral intake, chronic diarrhea and vomiting may predispose patients to prerenal azotemia and acute tubular necrosis. Furthermore, HIV-1 patients are frequently exposed to medications that can adversely affect renal function. For example, acute tubular necrosis can be caused by pentamidine, foscarnet, cidofovir, amphotericin B or aminoglycosides. Renal calculi and tubulointerstitial crystal deposition can be caused by indinavir. Many antibiotics such as trimethoprim sulfamethoxazole are capable of inducing interstitial nephritis (13).

Even after most acute causes of renal failure are ruled out, only approximately 50% of suspected cases are confirmed to be HIVAN after renal biopsy. Common alternate findings are mesangioproliferative glomerulonephritis and IgA nephropathy. Studies that have reported biopsies of patients with potential HIVAN have found a wide range of renal diseases such as amyloidosis, minimal change disease, diabetic nephropathy, allergic interstitial nephritis, and cryoglobulinemia, instead of HIVAN (4, 14–16). Therefore, for patients suspected of having HIVAN, it is important for a kidney biopsy to be performed, to establish the diagnosis.

Clinical Course and Prognosis

In the absence of treatment with highly active antiretroviral therapy (HAART) or angiotensin-converting enzyme (ACE) inhibitors, most patients with HIVAN progress to end-stage renal disease within weeks to months from the time of diagnosis (11). Mortality is generally a result of other AIDS-related complications. In an early study, Carbone et al. showed that the survival rates of HIVAN patients were similar to those of patients with AIDS (11). Mortality in patients with ESRD due to HIVAN is high (approaching 50% in one study) but is improving with the widespread use of HAART (8).

Epidemiology

In the United States, the current prevalence of HIVAN is probably underestimated, since the US Renal Data System (USRDS) only accounts for cases that have progressed to end-stage renal disease (1; Fig. 1). With the advent of HAART and ACE inhibitors, there are many cases of HIVAN now that do not progress to ESRD as rapidly as they did in the past. In order to determine the true prevalence, one study evaluated 557 HIV-1 seropositive patients using urinalysis. Those with > 1.5 g/day of proteinuria were biopsied. In this study, the incidence of HIVAN in African-American patients with HIV-1 was 3.5%; no cases were identified in non-black patients (16). A recent study reviewing autopsies of HIV-1 seropositive patients found that among black patients, 12% had HIVAN at the time of death. The higher prevalence of HIVAN in this series may be due to advanced AIDS in many of these patients (17).

With the continued increase of HIV-1 infection around the world, HIVAN is likely to become an increasingly prominent problem. In 2003 alone, more than 3 million people in sub-Saharan Africa were estimated to have been infected with the virus. Worldwide, only 7% of people who need anti-retroviral therapy have the means of obtaining it (18). This could translate into a large number of patients with end-stage renal disease due to HIVAN.

Pathology

Light microscopy of HIVAN biopsies is characterized by frequently collapsing focal glomerulosclerosis. The term “collapse” refers to an implosive retraction of the glomerular basement membrane. There is marked hypertrophy and hyperplasia of the overlying visceral epithelial cells. These cells may display mitotic figures and intracytoplasmic protein resorption droplets (14, 19; see Fig. 2a). Other histological findings include microcystic dilatation of the tubules. Microcysts are tubules that have at least three times the outer diameter of normal tubules. This is accompanied by atrophy and flattening of the tubular epithelial cells (20). Prominent lymphocytic infiltration of the interstitium is frequently present (see Fig. 2b). Electron microscopy may show numerous tubuloreticular structures in glomerular endothelial cells (14). On immunofluorescence, there may be staining for IgM, C3 and less frequently, C1 (9).

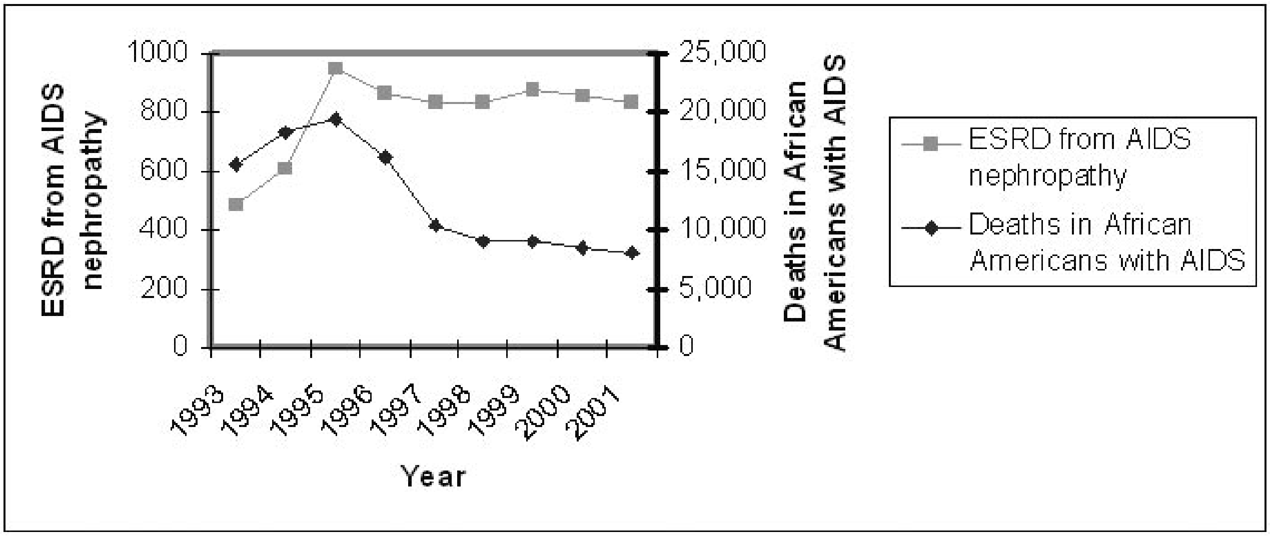

Fig. 1. Trends in ESRD due to HIV-associated nephropathy and mortality in African Americans with AIDS. U.S. Renal Data System, USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2004. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government (2).

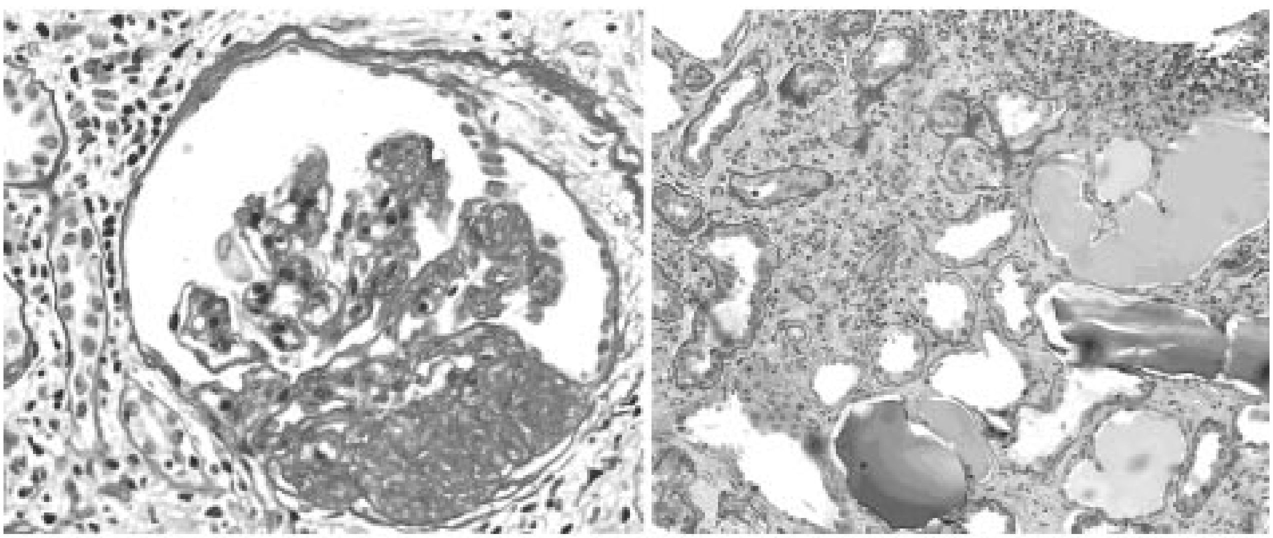

Fig. 2. Light microscopy from human biopsy with HIVAN. **A.** Characteristic collapsing focal segmental glomerulosclerosis with podocyte proliferation. **B.** Microcystic tubular dilatation and inflammatory interstitial infiltrates.

Pathogenesis

Animal studies have greatly added to our understanding of HIVAN pathogenesis. An HIV-1 transgenic mouse expressing a gag/pol deleted, replication-defective proviral construct develops renal disease very similar to HIVAN in humans, with proteinuria and progressive azotemia (21, 22). Studies using animal models of HIVAN suggest that the renal pathogenesis is due to viral infection of the renal cells rather than immune dysregulation in the setting of systemic HIV-1 infection. One study used reciprocal kidney transplantation between wild-type and HIV-1 transgenic mice to demonstrate the importance of viral gene expression in causing HIVAN. The HIV-1 transgenic mice that received transplants from nontransgenic littermates did not develop kidney disease, whereas normal non-transgenic mice that received transplants from HIV-1 transgenic mice did develop HIVAN. This suggests that renal transgene expression is a necessary component in the development of kidney disease (23).

In humans, the presence of HIV-1 in renal epithelial cells has been shown. One study examined human kidney biopsy samples from HIV-1 seropositive patients. Using *in situ* hybridization, HIV-1 RNA was detected in renal epithelial cells. The presence of HIV-1 was further confirmed using DNA in *situ* polymerase chain reaction (PCR). Of note, HIV-1 RNA and DNA were also detected in renal epithelia from several patients with undetectable viral loads, suggesting that renal cells may act as a reservoir for HIV-1 (15). Additional evidence for a renal reservoir of HIV-1 was provided by a case report of a patient who developed HIVAN with acute HIV-1 infection. Treatment with highly active antiretroviral therapy resulted in resolution of clinical and pathologic signs of the disease. However, renal epithelial expression of viral mRNA did not change following treatment (3). Marras et al. used laser-capture microdissection to remove infected renal tubular cells from 2 patients. Phylogenetic analysis of gp120 DNA sequences obtained from these cells and peripheral blood mononuclear cells from the same patients revealed evidence of tissue-specific viral evolution, suggesting that renal epithelial cells are able to support full viral replication (24). The mechanism of viral entry into renal epithelial cells is still unknown. CCR5 and CXCR4 are coreceptors to CD4 that mediate HIV-1 entry into lymphocytes. These receptors have not been demonstrated on renal epithelial cells *in vivo* (25).

Podocytes are the visceral epithelial cells that surround glomerular capillaries, forming an important part of the glomerular filter apparatus. They are terminally differentiated, quiescent cells that do not proliferate even in the setting of most glomerular diseases and podocyte injury. However, the collapsing glomerulopathy of HIVAN is characterized by marked podocyte dedifferentiation and proliferation. Studies have shown that HIV-1 infection leads to loss of differentiation markers in podocytes such as WT-1, synaptopodin, podocalyxin and common acute lymphoblastic leukemia antigen (CALLA). There is also an increase in proliferation markers such as Ki-67 and alterations in cell cycle regulators such as p27 and p57 (26 – 28). Conditionally immortalized HIV-1 transgenic podocytes proliferate *in vitro* in the presence of HIV-1 gene expression (29, 30).

Tubular microcyst formation is often the most prominent aspect of HIVAN pathology. Increased apoptosis and proliferation of tubular epithelial cells are seen in HIVAN (23, 26, 31). Microcyst formation and HIV-1 infection have been demonstrated in multiple segments of the nephron. One possible explanation for the development of microcystic disease in HIVAN is that HIV-1 infection initiates cyst formation by inducing proliferation of tubular epithelial cells. However, as the microcystic tubular epithelium becomes thin and atrophic, HIV-1 expression decreases, thereby decreasing epithelial proliferation and arresting cyst development at the microcystic stage (20).

Transgenic mice models have also been used to determine which HIV-1 genes are necessary to cause renal disease. HIV-1 encodes 9 different gene products, including the structural proteins gag, pol and env, regulatory proteins tat and rev, and accessory proteins vif, vpr, vpu, and nef. Studies using transgenic mice have implicated both nef and vpr in HIVAN pathogenesis (32, 33).

In vitro studies have confirmed the importance of nef in HIVAN pathogenesis. Infection of murine podocytes with an HIV-1 proviral construct with stop codons introduced at nef causes proliferation, anchorage-independent growth, loss of podocyte differentiation markers and increases in podocyte proliferation markers. On the other hand, infection of murine podocytes with full-length HIV-1 containing mutated nef fails to recapitulate the phenotypic changes found in HIVAN (29, 34, 35). Nef has multiple functional domains that can interact with cellular signal transduction molecules. Recent work has demonstrated that nef exerts its phenotypic changes in podocytes by activating the Src-Stat3 and Ras-c-Raf-MAPK 1,2 pathways (33).

Genetic Susceptibility to HIVAN

The apparent predisposition of patients of African descent to develop HIVAN suggests that host genetic factors are important determinants of whether an HIV-seropositive patient will develop HIVAN. Mice display a similar genetic predisposition to HIVAN. Certain mouse strains are susceptible to developing a HIVAN phenotype in the presence of an HIV-1 transgene, whereas other strains are resistant. Gharavi et al. used genome-wide linkage analysis to map genetic loci that are associated with the development of the HIVAN phenotype in mice (36). Several candidate loci have been identified, and attempts to determine the responsible genes within these loci are underway.

Treatment

HAART

The most compelling evidence for the efficacy of HAART in preventing progression of HIVAN to ESRD is that in the United States, the annual number of new patients whose ESRD is caused by "AIDS nephropathy" (the term used by the USRDS to identify patients with HIV-related renal disease) has remained relatively steady since 1995. This is in contrast to the steady rise in prevalence of HIV/AIDS in the general population, and the dramatic decrease in HIV/AIDS-related mortality in the U.S. This discrepancy suggests that HAART is indeed effective in preventing progression to end-stage renal failure in HIVAN patients. In a retrospective cohort study by Szczech et al. of 19 patients with HIV-related renal disease, patients receiving protease inhibitors had a significant reduction in the rate of decline of renal function (37). In one case report Winston et al. documented the resolution in clinical and pathological signs of HIVAN 15 weeks after the institution of HAART (3).

HAART may also prevent the development of HIVAN in at-risk groups. Lucas et al. evaluated a cohort of 3,976 at-risk patients in the Johns Hopkins HIV clinic database from 1989 to 2001. They identified 135 cases of HIVAN based on either clinical or pathological criteria. HAART was associated with a 60% reduction in risk for developing HIVAN (5).

ACE Inhibitors

There are several small studies suggesting a beneficial effect of ACE inhibitors on HIVAN. Wei et al. studied 44 patients with biopsy-proven HIVAN with serum creatinine < 2.0 mg/dL (0.7 – 1.4 mg/dL). All patients were offered treatment with the ACE inhibitor fosinopril. Twenty-eight patients assented to treatment with fosinopril 10 mg once daily, and the 16 patients who refused treatment acted as controls. After 5.1 years, all the patients on fosinopril had maintained stable renal function, whereas all patients in the control group were on dialysis. The study was limited by self-selection among the patients and concurrent medications were not controlled (38). Overall, the studies suggest that ACE inhibitors are beneficial for patients with HIVAN. However, a need remains for prospective studies to delineate the optimal role of ACE inhibitors in HIVAN.

Prednisone

Several studies have evaluated the efficacy of prednisone in the treatment of HIVAN. Smith et al. reported a series of 20 patients with advanced HIVAN who were treated with oral prednisone. In 17 patients, serum creatinine decreased significantly; but relapse was common after cessation of therapy. Six patients developed infectious complications while on steroid therapy (39). Eustace et al. evaluated a cohort of 21 patients with biopsy-proven HIVAN, 12 of whom were treated with prednisone. Multivariate analysis revealed that treatment with prednisone was associated with an odds ratio of 0.2 for developing ESRD. Infectious complications were not significantly elevated in the steroid treatment group; but once again relapse was common (40). Given the small size and lack of randomization of these studies, further evidence is needed before exposing patients with advanced HIV-1 infection to the potential side effects of prednisone.

Dialysis and Transplantation

In spite of a theoretical concern that hemodialysis may enhance white blood cell release of cytokines, thereby increasing viral replication, USRDS data does not show a survival advantage for peritoneal dialysis over hemodialysis (41). Unfortunately, survival of HIV-1 seropositive patients requiring renal replacement therapy is poor compared to HIV-1 seropositive patients not on dialysis and non-HIV-1 seropositive dialysis patients (42). With decreased morbidity and mortality in HIV-1 seropositive patients, kidney transplantation is now more frequently considered and performed by some transplantation centers. Roland et al. presented preliminary data of HIV-1 seropositive patients without a history of opportunistic infections, with CD4 T cell counts greater than 200 cells/mm^3 (480 – 1700 cells/mm^3) and with undetectable viral loads, who underwent solid organ transplantation. The patients were followed for only approximately 1 year, and data suggest that CD4 cell counts and plasma HIV RNA level suppression can be maintained in the setting of post-transplant immunosuppression in suitable patients. Patient and graft survival rates were similar to 1-year survival rates in the United Network for Organ Sharing (UNOS) database (43). A multicenter prospective study is currently underway to determine the safety and efficacy of renal transplantation in HIV-1 seropositive patients with ESRD.

Conclusion

HIVAN is the most common cause of chronic renal failure in HIV-1 seropositive patients and is especially prevalent among patients of African descent. Though HAART has dramatically reduced mortality of patients with HIV/AIDS, the incidence of ESRD due to HIVAN has remained stable and is likely to increase. HIV-1 infection of the renal epithelium is a critical component of HIVAN pathogenesis and also represents an important reservoir in which the virus may persist despite a lack of detectable virus in plasma. The efficacy of antiretrovirals, ACE inhibitors, and prednisone has been evaluated in small retrospective studies, but larger prospective studies of their value for the prevention and treatment of HIVAN are urgently needed.

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