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HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection

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HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection.

Background. Human immunodeficiency virus–associated nephropathy (HIVAN) can be the initial presentation of HIV-1 infection. As a result, many have assumed that HIVAN can occur at any point in the infection. This issue has important implications for appropriate therapy and, perhaps, for pathogenesis. Since the development of new case definitions for acquired immunodeficiency syndrome (AIDS) and better tools to assess infection, the relationship of HIVAN to the time of AIDS infection has not been addressed. In this study, we reassessed the stage of infection at the time of HIVAN diagnosis in 10 patients, and we reviewed all previously published cases applying the new case definitions to assess stage of infection.

Methods. HIVAN was confirmed by kidney biopsy in HIV seropositive patients with azotemia and/or proteinuria. $CD4^+$ cell count and plasma HIV-1 RNA copy number were measured. We also reviewed all published cases of HIVAN to determine if AIDS-defining conditions, by current Centers for Disease Control definitions, were present in patients with biopsy-proven HIVAN.

Results. Twenty HIV-1 seropositive patients with proteinuria and an elevated creatinine concentration were biopsied. HIVAN was the single most common cause of renal disease. $CD4^+$ cell count was below 200/mm^3 in all patients with HIVAN, fulfilling Centers for Disease Control criteria for an AIDS-defining condition. HIV-1 plasma RNA was detectable in all patients with HIVAN. In reviewing previous reports, an AIDS-defining condition was present in virtually all patients with HIVAN.

Conclusion. HIVAN develops late, not early, in the course of HIV-1 infection following the development of AIDS. This likely accounts for the poor prognosis noted in previous publications and has implications for pathogenesis. In addition, given the detectable viral RNA levels, highly active antiretroviral therapy is indicated in HIVAN. Highly active antiretroviral therapy may improve survival as well as alter the natural history of HIVAN.

Key words: AIDS, end-stage renal failure, highly active antiretroviral therapy, HIV-associated nephropathy, focal segmental glomerulosclerosis, virus.

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Human immunodeficiency virus–associated nephropathy (HIVAN) is the single most common cause of chronic renal disease in HIV-1 seropositive patients [1–4]. The incidence of HIVAN continues to increase [5], and we have calculated from the U.S. Renal Data System database that HIVAN is now the third leading cause of renal failure in African Americans between the ages of 20 and 64 [6]. Without a major change in the acquired immunodeficiency syndrome (AIDS) epidemic in general, nephrologists can anticipate that increasing numbers of HIVAN patients will be presenting to them in the future [6]. HIVAN is morphologically defined by a collapsing form of focal segmental glomerulosclerosis, glomerular visceral epithelial cell hypertrophy, and prominent tubulointerstitial infiltration with edema, fibrosis, and microcystic tubule dilatation [7, 8]. In the absence of specific therapy, HIVAN progresses to end-stage renal failure within weeks to months [9–13].

End-stage renal disease patients who are not infected with HIV have a median survival of approximately six years [14]. Median survival of new HIV seroconverters is 10 years [15], yet patients with HIVAN who come to dialysis have a mortality that approaches 50% per year [16]. In a review of 102 patients with biopsy-proven HIVAN, mortality rates at one and three years were 50% and 68%, respectively [17]. In this report and others, mortality has been especially high when the underlying HIV infection becomes symptomatic or progresses to an AIDS-defining condition [2, 3, 16, 18]. Prior to the era of potent, combination antiretroviral therapy, mortality rates in AIDS patients without renal disease were similar to those of patients with HIVAN—50% at one year and 70% to 85% at three years [19, 20]. These data suggest that patients with HIVAN have a clinical progression that is essentially equivalent to seropositive patients who develop an AIDS-defining condition.

The observation that the natural history of patients with HIVAN is similar to those with clinical AIDS is difficult to reconcile with the observation that HIVAN occurs at any stage of infection and can even occur early

in the course of HIV-1 infection [2–4]. Two hypotheses can be generated by these observations: (*a*) The development of nephropathy, or the progression to end-stage renal disease, in some way impacts the natural history of HIV-1. (*b*) HIVAN is, in essence, an AIDS-defining condition that presents late in the course of HIV infection and has a prognosis similar to any seropositive patient that develops AIDS.

In this study, we address these exclusive hypotheses by analyzing $CD4^+$ cell counts and viral burden in seropositive patients with renal disease. We find that an AIDS-defining condition, as currently defined by the Centers for Disease Control [21], predates the diagnosis of HIVAN in all patients. We conclude that HIVAN usually develops as a late complication of HIV-1 infection. This is an important observation for defining an optimal treatment(s) for patients with HIVAN, and it may have implications for disease pathogenesis.

METHODS

Human immunodeficiency virus-1 seropositive patients were eligible for enrollment into an Institutional Review Board (IRB)-approved protocol in which the diagnosis of HIVAN was confirmed by a percutaneous kidney biopsy. The patient population consisted of those referred for nephrologic consultation. Biopsies were performed when HIVAN was suspected based on the clinical criteria: urinary protein excretion exceeding 1 g/24 hr or the presence of azotemia not attributable to acute renal failure. Renal biopsies were processed for light microscopy, immunofluorescence, and electron microscopy according to standard techniques. HIVAN was diagnosed by the presence of focal segmental glomerulosclerosis combined with visceral epithelial cell hypertrophy, glomerular collapse, and interstitial infiltrates accompanying microcystic tubule dilation [1]. Plasma HIV-1 RNA was measured at the time of kidney biopsy using a commercially prepared quantitative reverse-transcriptase polymerase chain reaction assay (Amplicor; Roche Diagnostic Systems, Branchburg, NJ, USA). Measurements of $CD4^+$ cell counts were performed in the clinical immunology laboratory by immunophenotyping by flow cytometry using a Becton Dickinson FACScan (San Jose, CA, USA).

RESULTS

Over the course of 18 months between 1995 and 1997, 20 seropositive patients with chronic renal disease consented to biopsy. Their findings are summarized in Table 1. HIVAN was diagnosed in half of all patients, whereas various other causes of parenchymal disease were found in the remaining group. Mean values for serum creatinine, 24-hour urinary protein excretion, and $CD4^+$ counts were not different between patients with and without HIVAN. Nine patients with HIVAN and eight patients with other kidney diseases were African American, and the remaining were Hispanic. The age range was 24 to 58 years and was similar in both groups. In those with HIVAN, 50% were asymptomatic with regard to their HIV-1 infection and had suffered no opportunistic infections. By criteria prior to 1993, they would have been considered to have asymptomatic or early infection. By current criteria, these patients had AIDS because $CD4^+$ counts were less than 200 cells/mm^3.

At the time of biopsy, five patients with HIVAN were taking antiretrovirals, but none were receiving protease inhibitors. As shown in Table 2, plasma HIV-1 RNA was detectable in seven patients, ranging from 7.5×10^2

Table 1. Serum creatinine, protein excretion and $CD4^+$ cell count in human immunodefiency virus-1 (HIV-1) seropositive patients with HIV-associated nephropathy (HIVAN) and other forms of renal disease

Patient #	Diagnosis	Creatinine *mg%*	Urinary protein *mg/24 hrs*	CD4 *cells/mm^3*
1	HIVAN	5	4700	20
2	HIVAN	2.5	6100	10
3	HIVAN	1.6	1100	0
4	HIVAN	2.2	1100	200
5	HIVAN	2	7500	30
6	HIVAN	1.4	5300	0
7	HIVAN	3.5	12000	40
8	HIVAN	3.3	3700	160
9	HIVAN	1.8	1500	120
10	HIVAN	5.6	2500	20
Mean		2.9	4550	60
SE		0.5	1082	23
11	Amyloid	5	2000	150
12	Acute GN	1.7	970	160
13	Min change	2.2	1300	10
14	Diabetes	4	4600	270
15	Focal GN	2	1800	90
16	Global Scl	1.8	2900	0
17	Diabetes	2	4600	60
18	Cryoglob	1.5	9800	110
19	Cryoglob	1.8	1600	190
20	Acute GN	2		770
Mean		2.4	3286	181
SE		0.4	928	70

Abbreviations are: GN, glomerulonephritis; Min, minimal; Scl, sclerosis; Cryoglob, cryoglobulinemia.

Table 2. Plasma viral RNA levels (copies/ml) in HIVAN

Patient #	Diagnosis	Copies/ml plasma
1	HIVAN	1.2×10^3
2	HIVAN	2.3×10^5
3	HIVAN	3.6×10^6
4	HIVAN	7.5×10^2
5	HIVAN	1.2×10^3
6	HIVAN	1.3×10^6
8	HIVAN	5.8×10^3
10	HIVAN	6.2×10^4

Table 3. AIDS defining conditions in patients with biopsy-proven HIVAN

Author	*N* Patients	Stage of HIV infection
Rao et al, 1984	11	All with opportunistic infection
Carbone et al, 1989	26	Low T4 count in all patients
Strauss et al, 1989	5	Low $CD4^+$
Langs et al, 1990	15	All patients with clinical AIDS, ARC
Kimmel et al, 1996	18	$CD4^+$ cell count $<200/mm^3$ except one patient (235 cells/mm^3)
Smith et al, 1996	20	Highest $CD4^+$ count 160 cells/mm^3
Burns et al, 1997	20	15 with $CD4^+$ <200 cells/mm^3 liter
Lardi et al, 1997	102	Mean $CD4^+$ cell count 122 cells/mm^3

Data are from 9–13, 17, 23, 24.

to more than 3.6×10^6 copies. In three patients with HIVAN, HIV-1 RNA was relatively low (less than 2×10^3) but was easily detectable. There was no correlation between plasma HIV-1 RNA levels, antiretroviral treatment, or serum creatinine, but the number studied was too small to reach a valid conclusion.

We then applied current AIDS case definitions to all previous studies of HIVAN in which CD4 counts were available. Those reports are summarized in Table 3. There were no serologic markers for HIV-1 when HIVAN was originally described in 1984 [12, 22], and therefore, all patients in the original report had advanced AIDS with opportunistic infections. Of the subsequent studies, we found six in which individual CD4 counts were reported [9–11, 13, 23, 24]. Together with our patients, these reports comprise 114 patients with HIVAN. Although many patients were asymptomatic in terms of their HIV-1 infection, $CD4^+$ counts were less than 200 cells/mm^3 in all but six patients.

DISCUSSION

Following HIV-1 infection, $CD4^+$ cell depletion results from ongoing viral replication and occurs late in the natural history of the disease [25]. Recognizing that individuals with $CD4^+$ cell counts less than 200 cells/mm^3 are at high risk for HIV-1–related morbidity and mortality, the Centers for Disease Control revised the case definition for AIDS in 1993. As reported by several groups prior to 1993, HIVAN could present as the initial manifestation of HIV-1 infection in patients who were otherwise asymptomatic [2, 12, 18]. This provided the supportive evidence for the current clinical suggestion that it is not unusual for HIVAN to occur early in the course of HIV-1 infection [3, 4].

We explored whether the patients reported to have asymptomatic early disease would have fallen into today's case definition for AIDS. In seven patients whose HIVAN was reported as the initial clinical manifestation of HIV-1 infection, opportunistic infections developed within six months in five patients and within 13 months in the other two [26, 27]. In retrospect, it is most likely that these patients were late in their disease. Of the several patients in our series who were asymptomatic or whose nephropathy was the initial manifestation of HIV-1 infection, all were markedly immunosuppressed. Our review indicates that this has been consistent in virtually all previously reported cases of HIVAN. Additional indirect evidence supports the hypothesis that HIVAN is a late complication of HIV-1 infection. The average time from seroconversion to the AIDS-defining condition of a $CD4^+$ count less than 200 cells/mm^3 or an opportunistic infection is 8 to 10 years [15]. If HIVAN occurred early in HIV-1 infection, one would expect some patients to have a prolonged disease-free interval, but this has not been reported.

The degree of immunosuppression present in patients with HIVAN is associated with a poor prognosis and an extremely high risk of death from AIDS. This risk may explain the high mortality rate of HIVAN reported by most authors. Many of our patients were not receiving or were not taking an optimal antiretroviral regimen. The current standard of care for patients with low CD4 cell counts and detectable viral burden is highly active antiretroviral therapy (HAART) [25]. Because virtually all patients with HIVAN have low CD4 counts and/or detectable viral burden, HAART should be part of the standard therapeutic approach in HIVAN. In the past, failure to treat these patients aggressively with antiretroviral therapy may be related, in part, to misconceptions regarding the stage of HIV-1 infection as well as insufficient information as to the use of antivirals in patients with impaired renal function. Dose adjustments are required for many of the reverse transcriptase inhibitors, whereas the protease inhibitors are primarily cleared by the liver and require no dose adjustments [28, 29]. Despite complicating factors, the presence of HIVAN should not exempt a patient from receiving HAART.

We have shown that the overwhelming majority of patients develop AIDS before HIVAN is diagnosed. We believe that the high mortality rate is understandable in the context of advanced HIV-1 infection and that the treatment for HIVAN is incomplete in the absence of specific therapy aimed at reducing viral replication. Because, by design, our study sampled only those patients with clinically recognizable nephropathy, we cannot make a definitive statement as to whether markers of early nephropathy may have been present prior to the onset of AIDS in our patients and in others. In two of our patients in whom prior determinations could be made, proteinuria developed after the onset of clinical AIDS. Sufficient data were not available to render a valid conclusion in the others. Thus, important questions remain to be answered: Are certain lesions a precursor to HIVAN? Do any clinical markers predict early HIVAN? Do early markers develop prior to the onset of AIDS?

These questions could be answered in a carefully planned, prospective natural history study that includes renal biopsy confirmation. To our knowledge, such a study has not been performed.

One unanticipated finding from our study was the number of patients with presumptive HIVAN who had other glomerular lesions. Patients with HIVAN could not be distinguished from seropositive patients with other forms of glomerular disease based simply on quantitative protein excretion, degree of azotemia, $CD4^+$ count, or plasma viral RNA level. Other clinical parameters such as renal sonographic appearance or hematuria, which may be helpful in distinguishing HIVAN from other lesions in seropositive patients, were not sufficiently assessed in this study to determine their predictive value. Given the relatively wide range in glomerular filtration rate and protein excretion observed and the varying etiologies of kidney disease in the seropositive patient, a kidney biopsy should be performed to establish a definitive diagnosis. Biopsy confirmation is certainly necessary when defining the natural history of HIVAN, designing clinical trials, or proposing new therapeutic interventions.

We have suggested a pathogenic link between the late stages of HIV-1 and HIVAN. The clinical course of HIV-1 infection is dynamic. Early in infection, M-tropic viral strains predominate, whereas later, as symptoms of AIDS develop, T-tropic strains emerge [30]. As the disease progresses, the pattern of cytokine production shifts from Th-1 to Th-2 [31]. These dramatic changes in viral tropism and/or host response in the late stages of HIV infection could have a considerable impact on the development of HIVAN by predisposing to productive renal infection or by altering the renal response to injury [32].

In conclusion, the overwhelming majority of patients with HIVAN have an AIDS-defining condition once the diagnosis of HIVAN is established, even though many may be asymptomatic in terms of their HIV-1 infection. In the few patients who do not meet criteria for AIDS, we would recommend that the diagnosis of HIVAN be considered an AIDS-defining condition. Like the majority of similarly immunosuppressed HIV-positive patients, patients with HIVAN are at high risk for death from AIDS and should be treated aggressively with highly active antiretroviral therapy. It is possible that antiretroviral therapy may prolong time to dialysis, improve survival, or alter the natural history of HIVAN. These issues should be studied in prospective clinical trials.

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