HIV-Associated Nephropathy: Clinical Presentation, Pathology, and Epidemiology in the Era of Antiretroviral Therapy

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Summary: The classic kidney disease of human immunodeficiency virus (HIV) infection, HIV-associated nephropathy, is characterized by progressive acute renal failure, often accompanied by proteinuria and ultrasound findings of enlarged, echogenic kidneys. Definitive diagnosis requires kidney biopsy, which shows collapsing focal segmental glomerulosclerosis with associated microcystic tubular dilatation and interstitial inflammation. Podocyte proliferation is a hallmark of HIV-associated nephropathy, although this classic pathology is observed less frequently in antiretroviral-treated patients. The pathogenesis of HIV-associated nephropathy involves direct HIV infection of renal epithelial cells, and the widespread introduction of combination antiretroviral therapy has had a significant impact on the natural history and epidemiology of this unique disease. These observations have established antiretroviral therapy as the cornerstone of treatment for HIV-associated nephropathy in the absence of prospective clinical trials. Adjunctive therapy for HIV-associated nephropathy includes angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, as well as corticosteroids in selected patients with significant interstitial inflammation or rapid progression.

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Within a few years of the first published descriptions of the acquired immune deficiency syndrome (AIDS), kidney disease was recognized as a complication of infection with human immunodeficiency virus (HIV).[1-3] Early reports from New York and Miami described an aggressive form of collapsing focal segmental glomerulosclerosis (FSGS) in African Americans and Haitian immigrants with advanced AIDS. Now known as HIV-associated nephropathy (HIVAN), this unique kidney disease quickly became a leading cause of end-stage renal disease (ESRD) among young African Americans, paralleling the growth of the HIV epidemic in this population.[4,5] This review focuses on the clinical presentation, histopathology, and changing epidemiology of HIVAN in the era of combination antiretroviral therapy (ART).

CLINICAL PRESENTATION OF HIVAN

In 1984, physicians in New York City reported a series of patients with advanced AIDS and rapidly progressive glomerular disease.[1] All of the affected patients in this initial report were African Americans or Haitian immigrants, although the significance of race was not fully appreciated until several years later.[6] The classic clinical presentation of HIVAN was characterized by rapidly progressive renal failure, accompanied by moderate to nephrotic range proteinuria, bland urinary sediment, and ultrasound findings of large, highly echogenic kidneys. Progression to ESRD or death was nearly universal, and by 1999 "AIDS nephropathy" had become the third lead-

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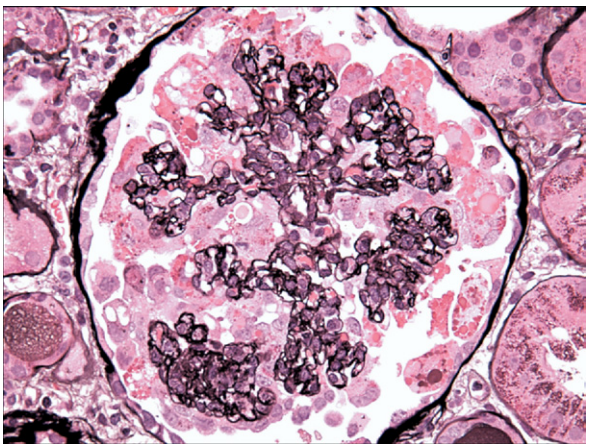

Figure 1. The glomerular capillary lumina are obliterated globally by collapse of glomerular basement membranes with hypertrophy and hyperplasia of overlying podocytes (Jones methenamine silver, 400×).

ing cause of ESRD among African Americans between the ages of 20 and 64 years.[4]

Although cases have been reported in the setting of asymptomatic HIV infection or acute HIV seroconversion,[7] HIVAN originally was described in patients with AIDS[1-3] and still generally is recognized as a complication of advanced HIV disease.[8] In a series of 107 HIV-infected patients who underwent kidney biopsy between 1995 and 2002, patients with classic HIVAN were more likely to have a CD4 cell count of less than 200 cells/mm^3 compared with patients with an alternative diagnosis (70% versus 31%), although there were no significant differences in HIV-RNA level or ART use.[8] The combination of nephrotic range proteinuria and a CD4 cell count of less than 200 cells/mm^3 was observed in half of the patients with HIVAN, compared with only 15% of those with another diagnosis. Although the combination of nephrotic range proteinuria and a CD4 cell count of less than 200 cells/mm^3 had limited sensitivity and specificity for the diagnosis of HIVAN, the absence of both findings may be more useful to exclude the diagnosis, with a negative predictive value reaching 90%.[8] In an earlier study, these investigators found that the degree of echogenicity on renal ultrasound also may have some predictive value for the diagnosis or exclusion of HIVAN, but only at the extremes of echogenicity. Kidney size did not distinguish HIVAN from other renal diagnoses in this study, possibly because patients with HIVAN presented with more advanced kidney disease.[9] Although clinical characteristics may help to refine the differential diagnosis in patients with contraindications to kidney biopsy, more than 30% of patients with suspected HIVAN based on these and other clinical criteria will have an alternative diagnosis on kidney biopsy.[8,10]

PATHOLOGY OF HIVAN

In the 1980s, the classic pathologic features of HIVAN began to emerge from autopsy and renal biopsy studies performed in institutions with a high prevalence of HIV/AIDS.[1,11-13] On gross examination at autopsy, the kidneys often were enlarged, pale, and swollen, with combined kidney weights as high as 500 g.[14] Renal enlargement may persist even in the setting of ESRD, owing to the presence of numerous tubular microcysts distending the parenchyma.

Light Microscopy

In the acute phase, untreated HIVAN typically manifests as a dramatic pattern of collapsing FSGS.[11,12] Glomerular capillary lumina are occluded by an implosive wrinkling and collapse of the glomerular basement membrane that more often is global rather than segmental, without predilection for the perihilar segments (Figs. 1 and 2). The acute nature of the glomer-

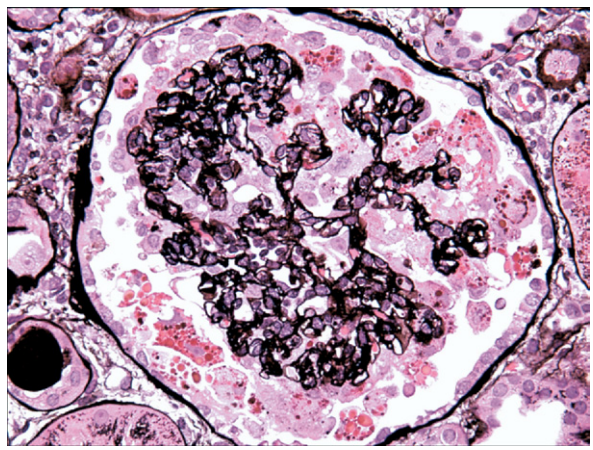

Figure 2. The podocytes surrounding the collapsed tuft form a corona of hypertrophied cells with numerous protein resorption droplets. Some of the podocytes appear detached from the tuft and suspended in the urinary space (Jones methenamine silver, 400×).

ular injury is evidenced by the lack of appreciable increase in intracapillary or mesangial matrix. The glomerular collapse is accompanied by prominent hypertrophy and hyperplasia of the overlying podocytes, which have enlarged, open vesicular nuclei with frequent nucleoli, occasional binucleate forms, and rare mitotic figures. Visceral epithelial cells may be so crowded as to obliterate the urinary space, forming pseudocrescents (Fig. 3). The podocyte cytoplasm typically is vacuolated, containing prominent intracytoplasmic protein resorption (hyaline) droplets (Fig. 4). As the lesions evolve, the glomerular tuft retracts into a tight solidified ball crowned by overlying enlarged, vacuolated, visceral epithelial cells. At this stage, the urinary space often appears dilated, containing a proteinaceous filtrate. Unlike FSGS, not otherwise specified (NOS), the collapsing variant of FSGS usually lacks hyalinosis, endocapillary foam cells, and adhesions to Bowman's capsule in the acute phase.[15] However, repeat biopsies and postmortem studies have shown that collapsing lesions may evolve into a more typical pattern of FSGS (NOS).

Tubulointerstitial disease is an invariable component of HIVAN and often appears out of proportion to the degree of glomerular injury. In addition to tubular atrophy, interstitial fibrosis, edema, and inflammation, there are widespread tubular degenerative and regenerative changes.[11,12] These include tubular epithelial simplification and hypertrophy with enlarged hyperchromatic nuclei, prominent nucleoli, mitotic figures, and focal apoptosis. The HIV-1 gene *Vpr* has been implicated in these changes, based on recent work showing that *Vpr* expression impairs cytokinesis in tubular epithelial cells in vitro.[16] Distended tubules containing loose proteinaceous casts form tubular microcysts, which may be numerous[10] (Fig. 5). Interstitial leukocytes consist predominantly of T lymphocytes, with renal CD4/CD8 ratios ranging from 0.35 to approximately 1.[12,17] Monocytes/macrophages, plasma cells, and B cells comprise a relatively small component of the infiltrate.

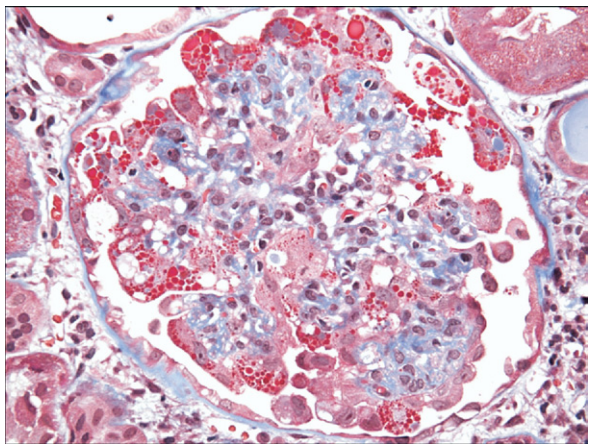

Figure 4. Overlying the collapsed tuft, the enlarged podocytes contain abundant trichrome-red protein resorption droplets (Masson trichrome, 400×).

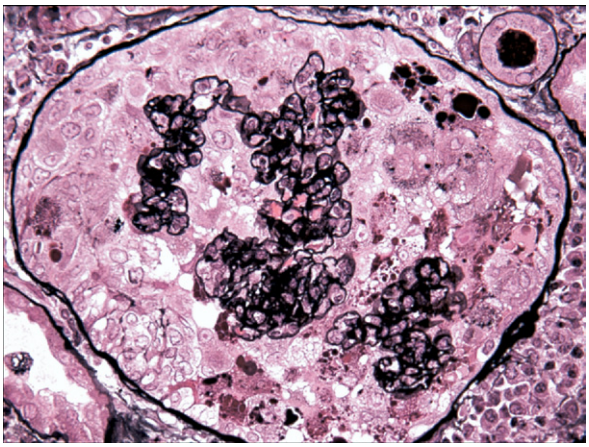

Figure 3. The podocyte hyperplasia forms pseudocrescents that obliterate the urinary space (Jones methenamine silver, 400×).

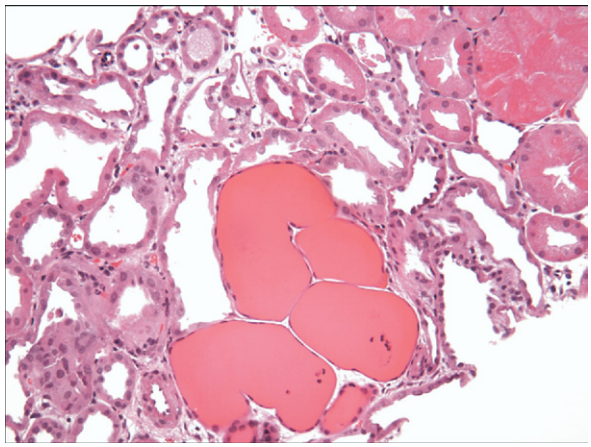

Figure 5. There are focally distended tubules forming microcysts that contain loose proteinaceous casts. Adjacent cortical tubules display degenerative changes (H&E, 200×).

Immunofluorescence

By immunofluorescence, there are segmental to global deposits of IgM, C3, and, less commonly, C1, in the collapsing segments. The noncollapsed glomeruli may display weaker mesangial staining for IgM and C3. Glomerular deposits of IgG and IgA are not identified. Visceral epithelial protein reabsorption droplets often stain for IgG, IgA, and albumin, with similar staining in the tubular epithelial protein droplets, consistent with increased intracellular protein trafficking.

Electron Microscopy

At the ultrastructural level, the collapsed lobules display wrinkling and little or no thickening of glomerular basement membranes. The overlying podocytes are markedly hypertrophied with severe foot process effacement, focal detachment, and increased numbers of organelles including electron dense protein resorption droplets, electron-lucent transport vesicles, and abundant rough endoplasmic reticulum (Fig. 6). The actin cytoskeleton usually appears disrupted, giving the cells a relatively open-appearing cytoplasm (Fig. 7). Noncollapsed capillaries also display severe foot process effacement, typically greater than 50%, and often exceeding 90% of the capillary surface area (Fig. 7). No electron dense deposits are observed, with the exception of rare small paramesangial electron densities corresponding to the mesangial deposits of IgM.

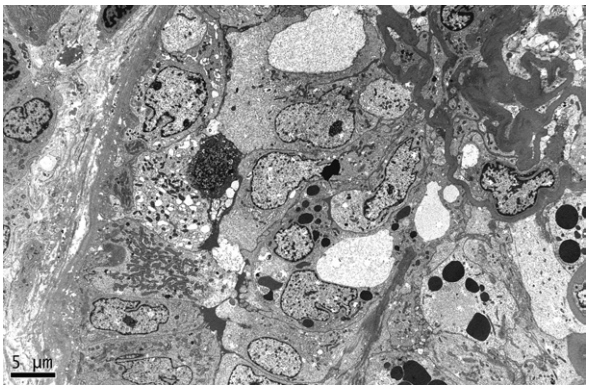

Figure 6. The collapsed capillaries have wrinkled glomerular basement membranes and are surrounded by hyperplastic visceral epithelial cells that obliterate the urinary space, in continuity with adjacent parietal epithelial cells (electron micrograph, 3,000×).

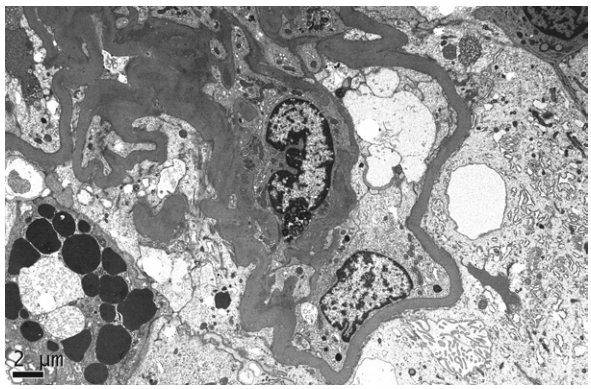

Figure 7. A high-power view shows podocyte hypertrophy with open-appearing cytoplasm and complete effacement of foot processes. One of the podocytes contains prominent intracytoplasmic protein resorption droplets (electron micrograph, 5,000×).

Endothelial tubuloreticular inclusions, also known as *interferon footprints*, commonly are identified as 24-nm tubular structures located in dilated cisternae of smooth endoplasmic reticulum (Fig. 8). These structures are a marker of HIV infection that can be found in endothelial cells and lymphocytes throughout the body. It is important to recognize that they are not a specific feature of the nephropathy and may be found in HIV-infected patients without HIVAN, as well as in patients with systemic lupus erythematosus, hepatitis C, and other viral infections. Although it has not been studied systematically, endothelial tubuloreticular inclusions appear to be less common in renal biopsy spec-

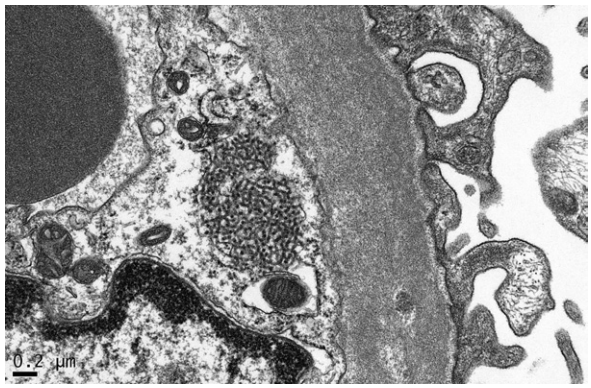

Figure 8. A large tubuloreticular inclusion is seen within a glomerular endothelial cell (electron micrograph, 40,000×).

imens from patients with HIVAN who are receiving ART. This observation is consistent with a reduction in viral burden and associated cytokine dysregulation that would be predicted to occur in the setting of ART. Endothelial tubuloreticular inclusions also are identified readily in collapsing glomerulopathy secondary to interferon therapy, but they are typically lacking in idiopathic collapsing FSGS, as well as those cases associated with pamidronate toxicity or parvovirus B19 infection.

Tubular epithelial cells often display enlarged regenerative nuclei with prominent nucleoli (Fig. 9), whereas the cells lining tubular microcysts typically are flattened (Fig. 10). Other ultrastructural findings in HIVAN include increased numbers of nuclear bodies within tubular and interstitial cells.[12,18] These intranuclear structures, which measure from 0.5 to 1.5 μm in diameter, are of uncertain significance. They are not specific for HIVAN, and may be up-regulated in diverse cell types in response to viral infections, hormonal activation, and neoplastic transformation. Granular degeneration of the nuclear chromatin of tubular and interstitial cells and the presence of cylindric confronting cisternae also may be observed.[12,18]

PODOCYTE DYSREGULATION IN HIVAN

In the course of normal glomerular development, podocytes undergo a choreographed program of proliferation and progressive maturation, culminating in a fully differentiated, quiescent phenotype. In the mature podocyte, the expression of

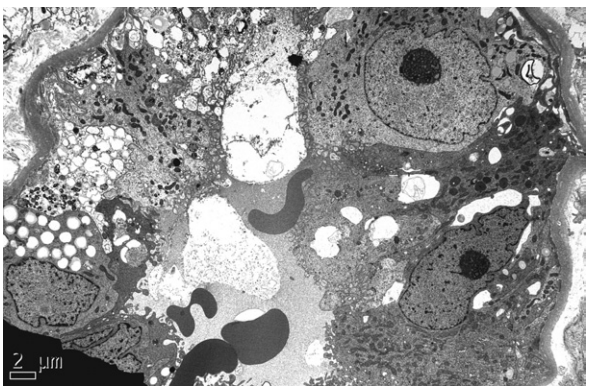

Figure 9. A tubule is lined by hyperplastic epithelial cells with enlarged regenerative nuclei containing prominent nucleoli (electron micrograph, 4,000×).

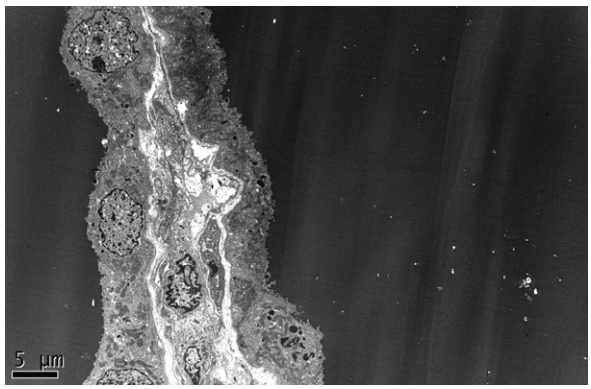

Figure 10. In an area of back-to-back tubular microcyst formation, the lining epithelial cells of 2 individual microcysts appear flattened and compressed by the voluminous proteinaceous electron dense cast material (electron micrograph, 3,000×).

WT-1, a zinc finger transcription factor that down-regulates proliferation, coincides with podocyte exit from the cell cycle, the expression of cyclin kinase inhibitors, and the acquisition of maturity markers.[19,20] In HIVAN and collapsing forms of primary FSGS, injured podocytes revert to a developmental program that includes down-regulation of cyclin kinase inhibitors, entry into the cell cycle, and loss of mature phenotypic markers.[21-24] Because it involves a loss of podocyte expression of the developmental regulatory protein WT-1, this altered podocyte phenotype has been termed *dysregulated*.[21]

The injured podocytes express the proliferation marker Ki-67 and lose maturity markers, such as CD10/CALLA, C3b receptor, GLEPP-1, podocalyxin, synaptopodin, and WT-1.[21] Of note, a reduction in synaptopodin expression, in contrast to other markers, also was observed in histologically unaffected glomeruli, suggesting that it precedes collapse.[21] By contrast, these podocyte phenotypic changes were not identified in minimal change disease or membranous glomerulopathy, despite similar levels of proteinuria and similar degrees of foot process effacement. In collapsed glomeruli, the endothelial expression of podocalyxin was preserved despite severe structural alterations of the capillary tuft and complete loss of podocyte expression.[21] These findings point to derangement of the podocyte phenotype occurring as a

primary event, rather than as a consequence of collapse.

Each phase of the cell cycle is governed by positive regulatory proteins (cyclins and cyclin-dependent kinases) and negative regulatory proteins (cyclin kinase inhibitors). Progression through the cell cycle requires the activation of cyclin-dependent kinases by complexing with specific partner cyclins. The Cip/Kip family of cyclin kinase inhibitors (p21, p27, and p57) function in both the G1 and S phase, and p21 also inhibits G2-/M-phase complexes. The cyclin kinase inhibitors p27 and p57 are expressed constitutively in mature podocytes, whereas p21 is not.[22] In HIVAN, as well as in idiopathic collapsing FSGS, there is decreased podocyte expression of p27 and p57, accompanied by de novo expression of p21 and Ki-67.[22,23] Interestingly, a generalized reduction in p27 and p57 can be identified in podocytes of some histologically unaffected glomeruli.[22] These findings support a paradigm wherein the reduction in p27 and p57 precedes the development of collapsing lesions and is permissive for the proliferative podocyte phenotype. Similar alterations in podocyte phenotype, as well as a dedifferentiated tubular epithelial phenotype, have been found in the HIV-1 transgenic murine model of HIVAN, supporting a pathogenic role for HIV viral gene expression.[24] The pathologic alterations can be attenuated or reversed by administration of the cyclin kinase inhibitor R-roscovitine, indicating a critical role for cell-cycle dysregulation in this model.[25] How specific viral proteins may mediate podocyte dysregulation is discussed in the article by Ross et al on HIVAN pathogenesis in this issue (p. 523).

The origin of the proliferating glomerular epithelial cells has been debated. A study of human HIVAN by Dijkman et al[26] has suggested that parietal epithelial cells proliferate to repopulate the injured visceral epithelial cells. In that study, many of the proliferating epithelial cells in areas of pseudocrescent formation expressed the parietal epithelial cell marker CK8 and lacked podocyte-specific markers. In addition, cell bridges to the CK8-positive parietal lining could be observed in serial sections, and no glomerular epithelial cells co-expressed podocyte markers and CK8.[26] These findings are consistent with emerging evidence that the parietal epithelium at the glomerular hilus may provide a niche for podocyte progenitor cells.[27] On the other hand, studies have clearly established the ability of podocytes to enter the cell cycle. Transgenic mice expressing HIV-1 *Nef* under the podocin promoter show expression of the cell-cycle markers Ki-67 and phospho-Stat3 in podocytes.[28] The relative contribution of podocytes and parietal cells to glomerular epithelial cell proliferation in HIVAN and other forms of collapsing glomerulopathy remains to be fully defined.

DIFFERENTIAL DIAGNOSIS OF RENAL BIOPSY FINDINGS

A biopsy picture of collapsing glomerulopathy is not specific for HIVAN. Differential diagnosis of the collapsing variant of FSGS includes primary (idiopathic) FSGS,[29] parvovirus B19 infection,[30] SV40 infection,[31] acute cytomegalovirus infection,[32] erythrophagocytosis syndrome,[33] interferon therapy,[34] pamidronate toxicity,[35] acute vaso-occlusive injury,[36] rare familial forms,[37] and glomerular injury in the renal allograft associated with microvascular disease.[38]

Renal biopsy in the HIV-infected patient is required to establish a diagnosis of HIVAN and to exclude other causes of renal dysfunction and proteinuria, including a variety of HIV-related glomerular diseases, non–HIV-related renal diseases, and medication nephrotoxicity, many of which are reviewed in detail in the articles by Cohen et al (p. 535), Fine et al (p. 545), and Atta et al (p. 563) in this issue. Other glomerular lesions encountered in the HIV-infected patient are listed in Table 1. Immune complex–mediated glomerular disease is more common in the Caucasian population, whereas HIVAN predominantly affects African Americans. It is particularly challenging for the renal pathologist to distinguish HIVAN from other forms of FSGS, including secondary FSGS from hypertensive arterionephrosclerosis or pre-existing primary FSGS, which also are more common in black patients. Recent biopsy series in HIV-infected patients indicate an increasing prevalence of FSGS (NOS) in parallel with a reduction in HIVAN, suggesting modifi-

Table. 1. Glomerular Lesions Occurring in HIV-Infected Patients

HIVAN (collapsing glomerulopathy)
FSGS NOS
Minimal change disease
Immune complex–mediated glomerulonephritis
Lupus-like nephritis
IgA nephropathy
Membranoproliferative glomerulonephritis (associated with hepatitis C or B)
Membranous glomerulopathy (associated with hepatitis B or C, or neoplasia)
Acute postinfectious glomerulonephritis
Fibrillary and immunotactoid glomerulonephritis (often associated with hepatitis C)
Diabetic nephropathy
Amyloidosis, AA type (associated with intravenous drug use)
Thrombotic microangiopathy

cation of the collapsing pattern of HIVAN by ART.[39,40] To illustrate the changing epidemiology of HIVAN, the renal biopsy incidence of HIVAN was 65% in a series of 112 patients reported in 1997,[41] but only 35% in a recent series of 152 biopsies.[39] Because endothelial tubuloreticular inclusions also appear to be reduced by ART, the biopsy picture of HIVAN may be attenuated in ART-treated patients, approximating the morphologic appearance of FSGS (NOS). In addition, as patients live longer with HIV infection, they may develop other non–HIV-related kidney diseases common in the aging population, such as diabetic nephropathy and arterionephrosclerosis of aging or hypertension, which also may show focal sclerosing features.

TREATMENT OF HIVAN

In the absence of randomized clinical trials, the treatment of HIVAN is based on small uncontrolled studies, epidemiologic data, and pathogenic insights. The pathogenesis of HIVAN is reviewed in the article by Ross et al in this issue (p. 523), and is known to involve direct HIV infection and gene expression in renal epithelial cells, as well as host factors that affect susceptibility. Consistent with the direct pathogenic role of HIV infection, the introduction of combination ART in 1996 was followed by a decline in the incidence of HIVAN[42,43] and in the number of new cases of ESRD attributed to AIDS nephropathy in the United States.[5] These suggestive epidemiologic data are supported by small uncontrolled studies showing improved renal survival with ART,[44,45] and by case reports documenting renal recovery and histologic improvement after the initiation of ART.[7,46] In a retrospective study of 42 patients with biopsy-proven HIVAN from 6 US academic medical centers, ART use was associated with delayed progression to ESRD (hazard ratio, 0.24; 95% confidence interval, 0.07-0.84).[44] A similar improvement in renal survival with ART was shown in a single-center retrospective study of 36 patients with biopsy-proven HIVAN (hazard ratio, 0.30; 95% confidence interval, 0.09-0.98).[45] Although these estimates were adjusted for demographic and clinical characteristics, it is likely that there also are important unmeasured differences between patients who received ART and those who did not receive ART in these nonrandomized studies.

Recognizing that randomized controlled trials comparing ART with placebo are no longer ethically tenable, recently updated expert guidelines consider HIVAN an indication for the initiation of ART, regardless of CD4 cell count.[47,48] The guidelines also recommend adjunctive therapy with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers as tolerated,[47] based on evidence of benefit from cohort studies in patients with HIVAN and from randomized

clinical trials in other glomerular diseases.[49] The addition of corticosteroids may be considered in patients with aggressive disease or a prominent interstitial inflammatory component, based on uncontrolled clinical studies and in vitro evidence that HIV infection induces a local inflammatory reaction in tubular epithelial cells.[50-52]

The management of ESRD in patients with HIV infection is discussed in the article by Sawinski et al in this issue (p. 581). With improvements in the survival of HIV-positive dialysis patients,[53] patients with HIVAN who are approaching ESRD should be offered a choice between hemodialysis and peritoneal dialysis, which offer similar survival in adults with HIV infection.[54] Selected patients with remote HIVAN and well-controlled HIV infection also may be candidates for kidney transplantation.[55]

EPIDEMIOLOGY OF HIVAN IN THE ANTIRETROVIRAL ERA

Although the incidence of ESRD attributed to HIVAN reached a plateau in the United States after the introduction of combination ART, 800 to 900 new cases are reported to the US Renal Database System (USRDS) each year, and the prevalence of HIV-related ESRD continues to increase.[5,56] At the end of 2005, more than 2,700 individuals were living with ESRD attributed to HIVAN in the United States, compared with only 150 cases at the end of 1990.[5,56] This trend is projected to continue, in large part because of improvements in the survival of HIV-positive dialysis patients, but also because of the disproportionate burden of HIV infection and AIDS among African Americans. Assuming a stable annual mortality rate of 24% and linear growth of the HIV epidemic among African Americans, it is projected that nearly 10,000 individuals will be living with ESRD attributed to HIVAN by the year 2020.[56] These projections were based on diagnoses of AIDS nephropathy reported to the USRDS at the discretion of the treating physician. Although these cases likely reflect a heterogeneous population of HIV-positive patients with HIVAN and other glomerular diseases, these projections underestimate the true prevalence of HIV infection in the ESRD population. Unfortunately, the USRDS no longer collects data on HIV infection as a comorbid condition in incident ESRD patients, and future estimates from the USRDS will be limited to ESRD that is attributed to HIVAN.

In addition to the continued growth of the HIV-positive ESRD population in the United States, there is also alarming potential for an epidemic of HIVAN in sub-Saharan Africa. Nearly 90% of the ESRD attributed to HIVAN in the United States occurs in African Americans,[5] and a similar racial predisposition has been observed in other countries.[57,58] Emerging data suggest a high prevalence of kidney disease among HIV-infected individuals in sub-Saharan Africa, ranging from 6% among Kenyan patients without other risk factors for kidney disease, to as high as 38% in a Nigerian cohort.[59-61] Although kidney biopsies are performed less frequently in resource-limited settings, HIVAN was the most common diagnosis identified in published biopsy series from Nigeria and South Africa.[60-62] With expanding access to ART and prolonged survival of HIV-infected patients, HIVAN likely will be an important contributor to the growing public health burden of chronic kidney disease in sub-Saharan Africa.[62,63]

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