Looking into the past and future of human immunodeficiency virus nephropathy

Human immunodeficiency virus-infected patients are at risk of developing several types of acute and chronic renal diseases [1–3]. Among them, HIV-associated nephropathy (HIVAN) has received significant attention because it is believed to be caused by the direct effects of HIV-1 on renal cells. Typically, HIVAN is defined as a combination of several pathologic renal lesions that include a collapsing form of focal segmental glomerulosclerosis, glomerular visceral epithelial cell hypertrophy, and prominent tubulointerstitial infiltration with edema, fibrosis, and microcystic tubule dilation [1–3]. These changes lead to renal enlargement and a rapid progression to end-stage renal disease. The mechanisms by which HIV-1 induces renal lesions are not clearly defined, and it is possible that reviewing the natural history of HIVAN may help to elucidate the most relevant pathogenic events producing HIVAN, as well as other renal diseases related to HIV-1 infection.

Since the early years of the AIDS epidemic, some studies have suggested that HIVAN could be an early manifestation of the HIV infection [1, 2]. In this issue of *Kidney International*, Winston, Klotman and Klotman review the timing for the diagnosis of HIVAN under the current definition for AIDS cases that the Centers for Disease Control established after 1993 [4]. They conclude that an overwhelming majority of HIV-infected patients develop HIVAN during the late stage of HIV infection. In addition, they show that 50% of HIV-infected patients who had a renal biopsy because of azotemia and/or proteinuria (more than 1 g per 24 hr) revealed histologic features consistent with other renal diseases.

This study raises several interesting issues. First, it demonstrates the importance of doing a renal biopsy to confirm the diagnosis of HIVAN and suggests that new clinical entities generated by other renal diseases that develop in the setting of HIV infection may be on the way. Thus, additional information is needed to define how HIV-1 modulates the outcome of other classic renal diseases.

Second, Winston et al stress the concept that HIVAN is a late, not early, manifestation of HIV infection. It could be argued, however, that if patients with early renal disease were found, perhaps some of them would have had CD4+ cell counts closer to normal. Because the criteria for renal biopsy appeared to include elevated serum creatinine, these patients would have been missed. Thus, is HIVAN a late manifestation of HIV infection, or was the diagnosis made too late? The authors do point out, however, that other studies have included patients with earlier renal disease, and they, too, have low CD4+ cell counts. Therefore, what are the early stages of HIVAN? Based on results derived from HIV-transgenic mice, the course of HIVAN could be divided in two stages [5]. The first stage is characterized by the induction of renal injury by HIV-1 genes, which is manifested clinically by moderate proteinuria but normal serum creatinine levels. The second stage could be defined by the rapid regenerative/proliferative renal response leading to kidney enlargement and rapid progression to end-stage renal disease. Although the first stage is probably driven by HIV-1 genes, the second stage is more likely driven by cytokines or growth factors released by injured or regenerating renal cells. In patients with HIVAN, these two stages are less clearly defined, as continuous changes in viral replication, the host immune response to HIV-1 or other infectious agents, and the recruitment of HIV-1–infected cells in the kidney play additional roles throughout the course of the disease. However, HIV-infected children may undergo long periods of moderate proteinuria (one to two years) before developing nephrotic syndrome or renal failure [6, 7]. During this time, the presence of microcysts in the urine sediment, persistent proteinuria, and enlarged echogenic kidneys in renal sonograms are useful clinical markers to predict the presence of HIVAN [7]. Nevertheless, even considering these clinical markers of HIVAN, our experience in HIV-infected children support the notion that HIVAN is a late manifestation of HIV infection [7]. Thus, Winston et al’s suggestion that changes in viral tropisms and host response that occur during the late stages of HIV infection may play a relevant pathogenic role in HIVAN may be clinically relevant. For example, it is possible that regenerating renal cells may up-regulate the synthesis of chemokine receptors and cell surface glycosphingolipids, which can facilitate the late infection of more renal cells by specific strains of HIV-1 [8–10].

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This process may amplify the renal damage induced by HIV-1 during the late stage of infection, triggering the regenerative/proliferative response typical of HIVAN.

Finally, because an overwhelming majority of patients with HIVAN showed CD4+ cell counts below 200/mm3, Winston et al suggest that all patients with HIVAN should be treated with highly active antiretroviral therapy. Future prospective clinical trials should determine whether this recommendation is valid for patients with HIVAN and higher CD4+ cell counts. Nevertheless, one could predict that if HIVAN is truly the consequence of HIV-induced cytotoxic effects on renal cells, early initiation of effective antiretroviral treatments should prevent the progression of HIVAN. On the other hand, similar antiretroviral treatments may be less effective during the late proliferative stage of HIVAN, as this stage is predominately driven by cytokines or growth factors [5]. Thus, more research is needed to define the pathways modulating the progression of HIVAN during both the early and late stages of the disease and to identify effective ways to control them. At the same time, ongoing clinical studies will determine the impact of the new antiretroviral treatments on the natural history of HIVAN.

In conclusion, Winston et al have taken a step toward improving our understanding of the natural history of HIVAN. They have stimulated us to look into the history of HIVAN and to think about its future. Hopefully, more clinical studies will follow their lead, and new treatments will emerge, improving the quality of life and clinical outcome of patients with HIVAN.

REFERENCES