

Immune Complex Renal Disease and Human Immunodeficiency Virus Infection

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Summary: Immune complex glomerulonephritis is a common diagnosis in renal biopsy series of human immunodeficiency virus (HIV)-infected patients. There are a variety of glomerulonephritides associated with HIV infection, including IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, lupus-like glomerulonephritis, immunotactoid glomerulopathy, and fibrillary glomerulonephritis. In addition, HIV-related proteins may be implicated in circulating immune complexes directly related to a response to the infection. In some cases, the relationship of the HIV infection to the glomerulonephritis is unclear. HIV infection is associated with the development of polyclonal hypergammaglobulinemia, which can promote the development of circulating immune complexes. It is not clear if HIV-associated glomerulonephritis is caused by the passive trapping of these circulating immune complexes or the in situ deposition of antibodies binding to HIV viral antigens. Some renal lesions that are seen in the setting of HIV infection more likely may be related to the presence of a co-infection such as hepatitis C virus infection. The optimal therapy for immune complex glomerulonephritis in the setting of HIV infection is unknown. Because of the underlying immunosuppressed state of many HIV-infected patients, caution with traditional cytotoxic therapies is advised. The role of antiretroviral therapy in modifying the course of these renal lesions is unclear.

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The most common renal histopathologic lesion associated with human immunodeficiency virus (HIV) infection is focal segmental glomerulosclerosis (FSGS).¹⁻¹⁰ However, in almost half of the patients in renal biopsy series, lesions other than classic HIV-associated nephropathy (HIVAN) are identified.¹⁻¹¹ HIV infection has been associated with a variety of immune complex-mediated glomerulonephritides including IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, lupus-like glomerulonephritis, and immunotactoid glomerulopathy (Table 1).¹⁻¹¹ Genetic and environmental factors may lead to racial disparities in the development of partic-

ular renal lesions. Immune complex renal disease may be more prevalent among Caucasians, whereas classic HIVAN is more likely in patients of African heritage.¹⁻⁸ The diverse renal manifestations that have been associated with HIV infection highlight the key role renal biopsy has in the management of HIV-infected patients with renal disease.

PATHOGENESIS

HIV infection often leads to the development of polyclonal hypergammaglobulinemia, and circulating immune complexes frequently are found in HIV-infected patients.¹²⁻¹⁸ Kimmel et al² showed that immune complex deposits, composed of HIV peptides and antibodies directed against these antigens, lead to the development of glomerulonephritis. Immune complex deposition may be related to an immunologic response to opportunistic infections that stems from the immunocompromised state, and may represent a form of postinfec-

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Table 1. Immune Complex Renal Diseases Associated With HIV Infection

HIV-associated immune complex renal disease
HIV-associated IgA nephropathy
Membranoproliferative glomerulonephritis
Postinfectious glomerulonephritis
Membranous nephropathy
Lupus-like glomerulonephritis
Cryoglobulinemic glomerulonephritis
Immunotactoid glomerulopathy
Fibrillary glomerulonephritis

tious glomerulonephritis.^{1,2,18} It also is possible that glomerulonephritis in the setting of HIV infection may be unrelated to the underlying viral infection, but rather shares the same pathogenic mechanisms as other glomerulonephritides that affect the general population.^{2,7,8}

One proposed mechanism for the development of glomerulonephritis in HIV-infected patients is passive trapping of immune complexes containing HIV antigens.^{2,18-21} In several well-characterized patients, the association with HIV infection has been established with certainty by showing circulating or tissue immune complexes consisting of HIV antigens, such as p24, gp41, and gp120, bound to IgG or IgA antibodies produced in response to these antigens.^{1,2,18,19,21} Alternatively, in situ immune complex formation, with circulating antibodies binding to HIV antigens deposited on glomerular cells, may play a causal role similar to the mechanism underlying other idiopathic glomerulonephritides.^{2,18,19,22,23} Research in HIV-infected patients to date cannot discriminate whether passive trapping of immune complexes or in situ antibody deposition leads to the development of glomerulonephritis.^{18,19} Cellular immune responses likely play a synergistic role in the development of glomerulonephritis in HIV-infected patients.²⁴⁻²⁶

EPIDEMIOLOGY

A renal biopsy series of 28 HIV-infected patients with nephrotic range proteinuria in Washington, DC, found a 28.6% prevalence of glomeru-

lonephritis.²⁷ More than half of the patients in this largely African American cohort had FSGS. A review of renal biopsies from HIV-infected patients around the world reinforces the notion that immune complex glomerulonephritis is a relatively frequent histologic diagnosis, and that it may be more common among Caucasian patients than those of African heritage.

In a series of 60 renal biopsies from HIV-infected patients at a single center in Paris, 10 cases of lupus-like glomerulonephritis and 4 cases of IgA nephropathy were identified.⁵ Classic FSGS lesions were found in 43% of patients, and were more common in black patients, whereas the majority (52%) of patients with immune complex glomerulonephritis were Caucasian. In a smaller series of 17 patients from a London hospital, FSGS made up approximately 40% of the diagnoses. Other diagnoses included IgA nephropathy, MPGN, hemolytic uremic syndrome, and interstitial nephritis.¹⁰ In contrast, there were no cases of FSGS in a largely Caucasian cohort of 26 HIV-infected patients from 3 hospitals in northern Italy. Postinfectious glomerulonephritis was the most common finding, identified in 6 patients. Other diagnoses included mesangial proliferative glomerulonephritis, lupus-like glomerulonephritis, IgA nephropathy, and minimal change disease.²⁸

In non-European settings, a small biopsy series from Brazil included 2 cases of minimal change disease and 3 cases of classic FSGS, the latter occurring in black patients.²⁹ A series of 26 biopsies in HIV-infected patients in Thailand showed no cases of classic HIVAN lesions.⁹ Seventeen patients had mesangial proliferative glomerulonephritis. Other diagnoses included IgA nephropathy, diffuse proliferative glomerulonephritis, membranous nephropathy, and MPGN. These findings emphasize the frequency of glomerulonephritis in HIV-infected patients in populations of non-African ethnicity.

In a multicenter observational study that included 89 HIV-infected patients who underwent renal biopsies in the United States, 50% of the patients had a diagnosis other than HIVAN.⁶ Patients with lesions other than HIVAN tended to have a more favorable renal prognosis, and were more likely to be Caucasian, have higher CD4 counts, and have co-existent hepatitis infection.

Over the past several years, there has been increasing research dedicated to the AIDS epidemic in sub-Saharan Africa, where approximately 25 million people are estimated to be living with HIV/AIDS.³⁰ In a study of 176 HIV-infected patients in Israel, 72% of whom were originally from Ethiopia, no patient fulfilled pre-defined clinical criteria for classic HIVAN.³¹ Although this study was severely limited by the lack of biopsy data and small sample size, it highlighted the potential diversity of renal lesions that may be seen even among HIV-infected individuals from Africa.

In a series of 104 HIV-infected patients from South Africa with renal biopsies between 2003 and 2004, 20% had an HIV immune complex-mediated renal disease.³² Approximately one third of the patients had classic FSGS lesions. This proportion is somewhat lower than that reported in other series, which largely were composed of African American patients, and raises the possibility of separate environmental factors that may predispose people of African descent to the development of HIVAN. The increased prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection on the African continent also may contribute to the higher rate of immune complex-mediated glomerulonephritis in this series.

In contrast, another recent renal biopsy series of 30 HIV-infected patients from South Africa found a significantly higher prevalence of HIVAN, which was observed in 83% of patients.³³ MPGN was found in 2 patients and interstitial nephritis was found in 3 patients.³³ Four patients had evidence of membranous nephropathy superimposed on HIVAN.³³ These disparate results from 2 centers in South Africa emphasize the limitations of drawing significant epidemiologic conclusions from single-center studies with small sample sizes. Nevertheless, the data provide insight into the growing HIV epidemic in Africa and highlight the importance of conducting larger studies.

HIV IMMUNE COMPLEX GLOMERULONEPHRITIS

HIV-infected patients with immune complex-mediated glomerulonephritis often present with hypertension, an active urine sediment,

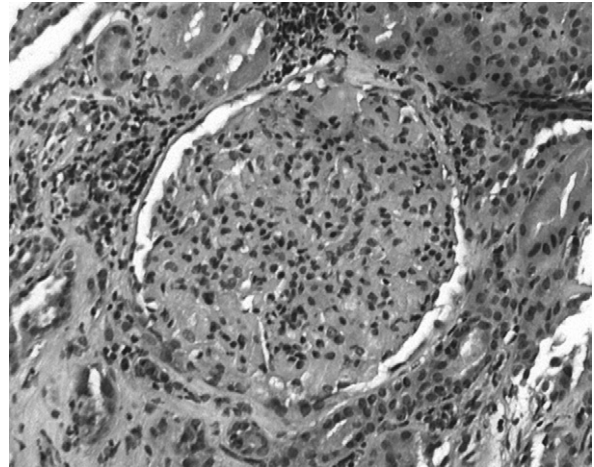


Figure 1. HIV-associated immune complex glomerulonephritis. Kidney biopsy from a patient with HIV infection, nonnephrotic range proteinuria, and hematuria. The glomerulus shows increased cellularity, predominantly within the mesangium. There is patchy congestion of glomerular capillaries without neutrophilic infiltration, fibrinoid necrosis or glomerulosclerosis. Hematoxylin-eosin stain, 40 \times objective magnification. Figure courtesy of Dr. David Kardon.

proteinuria, and renal insufficiency.^{1,2,19,34} Urinalysis typically reveals hematuria, and occasionally red blood cell casts.^{1,2,19,34} Low serum complements also may be seen.^{1,2,19,34} If patients display any of these clinical features, a renal biopsy should be strongly considered.

There is a spectrum of pathology associated with HIV immune-mediated glomerulonephritis (Fig. 1). Nochy et al⁵ categorized several major types of renal pathology: a “diffuse exudative endocapillary proliferative form” or “postinfectious form”; lupus-like glomerulonephritis with “diffuse endocapillary proliferative changes, wire loops, hyaline thrombi in capillary lumina,” and mesangial, subendothelial, and subepithelial immune deposits; and a hybrid form that includes changes consistent with both FSGS and immune complex renal disease. It is unclear if this final type represents 2 distinct pathologies or rather may be a more advanced form of immune complex renal disease that has progressed to focal segmental sclerosis in portions of glomeruli.

Similar to classic HIVAN, common findings include podocyte hyperplasia and fibrocellular crescents, microcystic tubular dilatation, and an interstitial inflammatory infiltrate made up of

macrophages and lymphocytes with occasional plasma cells, polymorphonuclear leukocytes, and eosinophils.^{19,25,34} HIV-infected patients with immune complex renal lesions have been shown to have a greater number of B cells infiltrating the tubulointerstitium compared with patients with classic HIVAN.²⁴ Electron microscopy may reveal mesangial, subendothelial, intramembranous, and subepithelial electron dense deposits.^{19,34} Similar to classic HIVAN, tubuloreticular inclusion bodies may be seen.

Kimmel et al² studied 4 HIV-infected patients with characteristic features of an immune complex-mediated renal disease. Circulating immune complexes were identified from the serum of all 4 patients.² These same immune complexes were eluted from the renal biopsy tissue in 3 of the patients in higher concentrations compared with plasma.² HIV antigens were found in the eluates of glomeruli of all 4 patients.²

In contrast to treatment of classic HIVAN, the role of antiretroviral therapy (ART) in delaying progression of immune complex renal disease in HIV-infected patients is unclear. Szczech et al⁶ did not find an effect of ART on progression of non-HIVAN renal disease in their multicenter cohort. The nephrotoxic potential of ART regimens must be considered. The renal disease may be related to another process, such as HBV or HCV co-infection, and there are cases in which the renal disease has been dissociated from HIV infection. This last point must be balanced, acknowledging that the nephropathy, even if seemingly unrelated to HIV infection after appropriate investigation, occurs in an immunocompromised host with immune dysregulation. Immunosuppressive strategies that treat the specific glomerular syndrome should be considered carefully, but outcomes have been variable.^{6,20,35} The risk of immunosuppressive agents in an immunocompromised patient must be weighed against the risk of progression to end-stage renal disease and the associated complications of nephrotic syndrome.^{2,36} Whenever possible, conservative antiproteinuric strategies with angiotensin-converting enzyme inhibition (ACEI) or angiotensin II receptor antagonists (ARB), blood pressure

control, and statin therapy should be maximized before considering cytotoxic agents, although this recommendation is not evidence-based.^{20,35,37}

LUPUS-LIKE GLOMERULONEPHRITIS

There have been several reports of HIV-infected patients who develop a glomerulonephritis with histologic features similar to systemic lupus erythematosus nephritis.^{4,5,38} Nochy et al⁵ found 10 cases of lupus-like glomerulonephritis in their series of 60 HIV-infected patients from Paris. Haas et al⁴ identified 14 cases of lupus-like glomerulonephritis out of 77 renal biopsies performed in HIV-infected patients over a 5-year period in Baltimore. The histopathology is characterized by focal and diffuse proliferative glomerulonephritis on light microscopy.^{4,5} Immunofluorescence is unique with a “full house pattern” of C1q, IgG, IgM, IgA, C3, lambda, and kappa deposits.^{4,5} The clinical signs usually include nephrotic range proteinuria and severe renal failure.⁴ Patients with this form of glomerulonephritis typically are resistant to therapy, test negative for antinuclear antibodies and anti-DNA antibodies, and have a poor 1-year renal survival.⁴ Thirteen of 14 cases of lupus-like glomerulonephritis in the Baltimore cohort were African American,⁴ which runs counter to the notion that Caucasians are more likely to develop immune complex glomerulonephritis.^{4,38} The relationship of this disorder to HIV infection remains unknown, and the proper therapy for such patients remains unclear and largely unevaluated.

IgA NEPHROPATHY

There have been a number of reports of IgA nephropathy occurring in HIV-infected patients,^{1,20,21,35,37,39-44} primarily in Caucasian or Hispanic patients.^{1,21,40,42-44} In 4 patients with HIV infection and biopsy-proven IgA nephropathy, tubuloreticular inclusion bodies were observed in glomerular endothelial cells.²¹ HIV antigens were not isolated from the renal biopsies, however, IgA antibodies to specific HIV antigens were detected.²¹ In a multicenter biopsy series, there was a 1.1% prevalence of IgA nephropathy among 89 HIV-infected patients.⁶

The true prevalence of IgA nephropathy in HIV-infected patients may be underestimated because the indolent course likely leads to a lower number of renal biopsies.³⁴ In a post mortem analysis, there was an 8% prevalence of IgA mesangial deposits among patients who died from complications of HIV infection.⁴¹ The significance of these lesions, and whether they constitute IgA nephropathy, is unclear.

Similar to other forms of HIV-associated glomerulonephritis, the hypergammaglobulinemic state may play a role in the development of nephritogenic IgA antibodies.^{2,12-17} Kimmel et al¹ reported 2 cases of IgA nephropathy in HIV-infected patients who were shown to have immune complexes composed of idiotypic IgA antibodies reacting with IgG and IgM antibodies against HIV p24 and gp120 antigens. Idiotypic antibodies may play a role in the pathogenesis of IgA nephropathy in the general population.^{1,45,46} These IgA antibodies also were identified in the eluates of renal biopsy specimens from these HIV-infected patients, establishing a causal link between the HIV infection and IgA nephropathy in these cases.¹ The production of idiotypic antibodies may be secondary to dysregulation of the immune system associated with HIV infection, a response to anti-HIV antibodies, or continued exposure to HIV-associated peptides.¹

The pathology of IgA nephropathy includes mesangial matrix expansion and hypercellular glomeruli with diffuse or segmental proliferation.^{1,21,40} Crescents are seen occasionally.^{1,21,34,40} The diagnosis is confirmed by immunofluorescence staining revealing a predominance of IgA.¹ There is often co-deposition of C3, IgM, and, less frequently, IgG.^{1,21,34,40} Electron microscopy may reveal mesangial and peripheral capillary wall electron dense deposits and tubuloreticular inclusion bodies within endothelial cells.^{21,34}

The clinical presentation of IgA nephropathy may differ from classic HIVAN. Typical clinical findings suggestive of IgA nephropathy include hematuria, an active urine sediment including red blood cell casts, and subnephrotic or nephrotic range proteinuria.³⁴ The progression to end-stage renal disease also may be slower.^{2,20,21,34}

Increased serum IgA levels are nonspecific and may be found in other HIV-infected patients.³⁴

Data on therapy for IgA nephropathy in the setting of HIV infection are limited to case reports.^{37,40,47} Despite limited evidence in HIV-infected patients, treatment of patients with IgA nephropathy should include conservative medical therapy with ACEIs or ARBs.³⁷ If the disease is progressive despite optimization of blood pressure control with ACEIs or ARBs, the use of immunosuppressive agents can be considered. However, the risks of toxicity should be strongly weighed against any potential benefits of therapy. The independent role of ART in slowing the rate of progression of IgA nephropathy is unclear. Larger prospective randomized controlled trials are needed to determine the optimal therapy of IgA nephropathy in HIV-infected patients.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

There have been several reports of MPGN occurring in the setting of HIV infection. MPGN may occur as an isolated idiopathic lesion or as the histopathologic manifestation of a postinfectious glomerulonephritis. Patients with HIV infection are predisposed to opportunistic infections that may have renal manifestations,⁴⁸⁻⁵³ and also share common risk factors that predispose them to HCV and HBV co-infection.^{54,55} Both HCV and HBV infection have been associated with the development of MPGN.^{54,55}

MPGN also may result from the use of therapeutic agents, in particular antiviral agents. Kimmel et al⁸ reported a case of MPGN in an HIV-infected patient after treatment with interferon. Immunochemical analysis of renal biopsy tissue revealed a single circulating immune complex with IgG antibody bound to an antigen that later was identified as interferon-alfa.

Therapeutic options for MPGN should first focus on identifying any potential secondary causes, including infection, neoplasia, or other autoimmune diseases, before considering intensive immunosuppressive therapy. Treatment of underlying infections may improve or even reverse the postinfectious variants of MPGN.⁵⁶ As with other forms of glomerulonephritis in the setting of HIV infection, the risk of immunosup-

pression must be weighed carefully against the limited data regarding benefits.

MEMBRANOUS NEPHROPATHY

There have been several case reports of membranous nephropathy in the setting of HIV infection.^{7,36,57,58} The significance of these renal lesions and their relationship to HIV infection is unclear. Several patients had concomitant HBV or HCV infection, which has been associated with the development of membranous nephropathy (Figs. 2 and 3).⁵⁹⁻⁶¹ In one case of an HIV-HBV co-infected Caucasian patient with biopsy-proven membranous nephropathy without features of HIVAN, there was resolution of the nephrotic syndrome with clearance of the HBe antigen.⁷

HIV AND HCV CO-INFECTION

HCV infection in the absence of HIV infection has been linked to the development of MPGN.⁶² Several cases and case series have identified patients with MPGN in the setting of HIV and HCV coinfection (Figs. 4 and 5).^{3,63} The relationship between the renal disease, the viral infection, and the immunologic response in these cases often is unclear. Patients with kidney disease who are co-infected with HIV and HCV may have a worse renal prognosis,^{6,63} al-

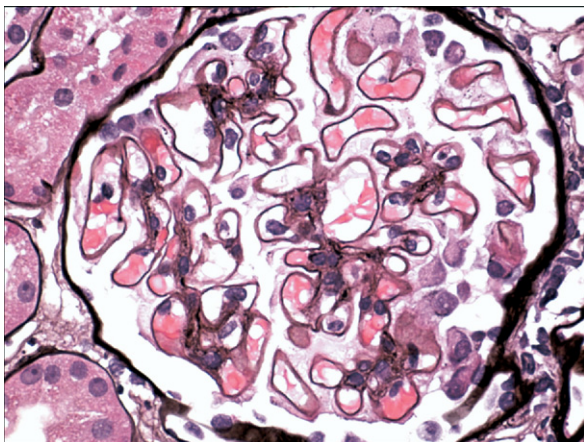


Figure 2. Membranous glomerulopathy in a patient co-infected with HIV and HCV. The glomerulus is normocellular with global thickening of the glomerular basement membranes and focal short spike formation. There is diffuse podocyte swelling. Jones methenamine silver, 400 \times . Figure courtesy of Dr. Vivette D'Agati.

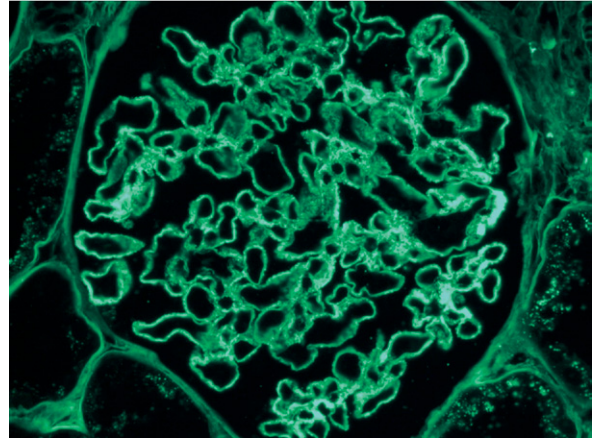


Figure 3. Membranous glomerulopathy in a patient with HIV and HCV co-infection. Immunofluorescence staining for IgG shows global granular staining of the glomerular capillary walls in a subepithelial distribution, with sparse segmental mesangial deposits. Immunofluorescence, 400 \times . Figure courtesy of Dr. Vivette D'Agati.

though data are limited. These patients are more likely to have used intravenous drugs and are more likely to have a diagnosis of MPGN as opposed to FSGS.^{3,63,64} Other forms of glomerulonephritis also have been observed in patients with HIV and HCV co-infection.^{3,64-68} Studies have not proved a causal role for HCV in the development of glomerulonephritis in co-infected patients.

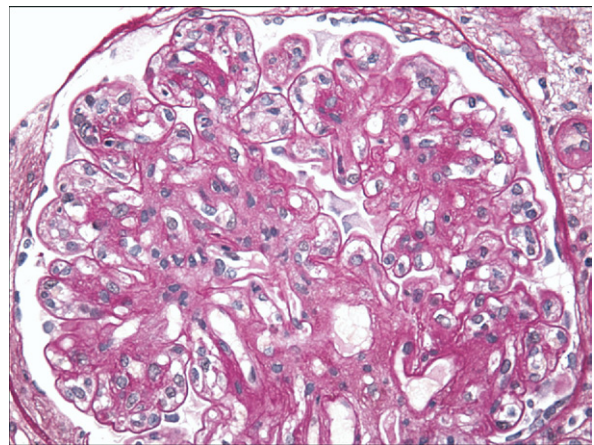


Figure 4. Membranoproliferative glomerulonephritis in a patient co-infected with HIV and HCV. The glomerular capillary lumina are occluded by global endocapillary hypercellularity including many infiltrating mononuclear leukocytes, with mesangial matrix expansion, accentuated lobularity, and segmental double contours. Periodic acid Schiff, 400 \times . Figure courtesy of Dr. Vivette D'Agati.

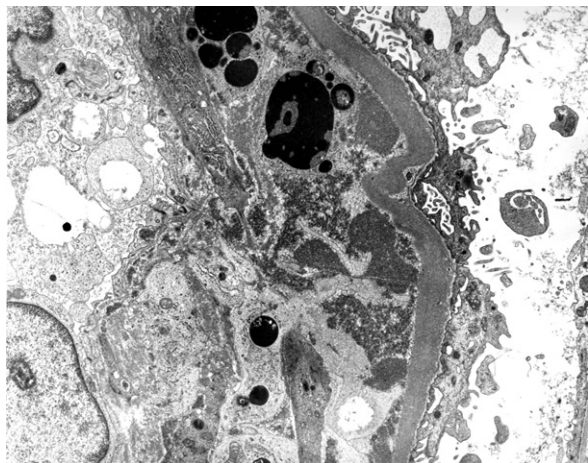


Figure 5. Membranoproliferative glomerulonephritis in a patient with HIV and HCV co-infection. Electron microscopy reveals subendothelial granular electron dense deposits and intracapillary infiltration by monocytes/macrophages with prominent phagolysosomes. There is overlying foot process effacement. Electron micrograph, 4,000 \times . Figure courtesy of Dr. Vivette D'Agati.

There should be a low threshold for renal biopsy in patients with evidence of renal injury and concomitant HIV and HCV co-infection. Optimal therapy for renal disease in co-infected patients is unclear, but likely includes treatment for both HIV and HCV infection. Treatment of HCV infection poses unique challenges in patients with reduced glomerular filtration rate because of the increased risk of drug toxicities.^{55,69} Randomized controlled trials are needed urgently to establish therapy for such patients.

CRYOGLOBULINEMIC GLOMERULONEPHRITIS, IMMUNOTACTOID GLOMERULOPATHY, AND FIBRILLARY GLOMERULONEPHRITIS

There have been several cases of cryoglobulinemic glomerulonephritis reported in the setting of HIV infection.¹⁹ Many of these patients have underlying HCV co-infection and cryoglobulinemia.^{70,71} The general impression is that cryoglobulinemia is a less frequent occurrence in patients with HIV mono-infection.⁷⁰

There also have been sporadic reports of immunotactoid glomerulopathy and fibrillary glomerulonephritis in the setting of HIV infection.^{65,68} The pathogenic significance and relationship to HIV infection are unclear. These

conditions also are associated with HCV infection and may be more common in co-infected patients.⁶⁶ The expression of these diseases in the setting of HIV infection also may be related to underlying immune dysregulation.

CONCLUSIONS

There are a variety of renal manifestations associated with HIV infection. Several renal biopsy series of HIV-infected patients with kidney disease report a high prevalence of glomerulonephritis, highlighting the key role of renal biopsy. Glomerulonephritis appears to be more common among Caucasians, although recently published renal biopsy series from the United States and South Africa have shown a high prevalence of HIV-associated glomerulonephritis in patients of African heritage. The modifying role of ART in the course of glomerulonephritis is unclear. Only biopsy and immunochemical analysis, usually performed on a research basis, can definitively establish the relationship between glomerulonephritis and HIV infection in an individual patient. Additional research is needed to evaluate the pathogenesis, epidemiology, and optimal treatment of glomerulonephritis in the setting of HIV infection.

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