Kidney International, Vol. 67 (2005), pp. 1381–1390

HIV-associated immune complex glomerulonephritis with "lupus-like" features: A clinicopathologic study of 14 cases[1]

Mark Haas, Sadhana Kaul, and Joseph A. Eustace

Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland

HIV-associated immune complex glomerulonephritis with "lupus-like" features: A clinicopathologic study of 14 cases.

Background. While the most common glomerular lesion associated with human immunodeficiency virus (HIV) infection is collapsing focal segmental glomerulosclerosis (FSGS) [HIV-associated nephropathy (HIVAN)], immune complex-mediated forms of glomerulonephritis have been increasingly reported. One form of glomerulonephritis that has been described in the HIV-infected population is immune complex glomerulonephritis with "lupus-like" features, characterized by histologic, immunohistologic, and ultrastructural features resembling lupus nephritis, but occurring in patients without evidence of systemic lupus erythematosus (SLE). Data regarding clinical outcomes in patients with this form of glomerulonephritis are very limited.

Methods. We reviewed pathology reports for all native renal biopsy specimens from HIV-positive patients processed at our center from January 1999 through December 2003. Of 77 total specimens, 14 met the following criteria for lupus-like glomerulonephritis: (*1*) immunofluorescence microscopy showed granular glomerular staining for IgG, IgA, IgM, C3 and C1q, with ≥1+ (0 to 4+ scale) staining for C1q; and (*2*) the patient's serum was negative for antinuclear antibodies (ANA), or weakly positive (titer ≤1:80) for ANA and negative for antidouble-stranded DNA.

Results. Clinically, ten of the 14 patients with lupus-like glomerulonephritis presented with nephrotic syndrome, all had microscopic hematuria, and nine had serum creatinine >3.0 mg/dL. All but one were African American. Histologically, seven biopsies showed diffuse proliferative glomerulonephritis, six focal proliferative glomerulonephritis, and one membranous nephropathy. All but two biopsies showed moderate or severe chronic change, and three showed concurrent HIVAN. Ten of the 14 patients developed end-stage renal disease (ESRD) within 1 year of the biopsy. Nine of these ten patients presented with proteinuria >5.0 g/24 hours and nephrotic syndrome, while three of four patients who did not develop ESRD had proteinuria ≤3.0 g/24 hours.

Conclusion. Lupus-like glomerulonephritis, defined by immunohistologic features and absence of serologic evidence of SLE, is not an uncommon form of glomerular disease in HIV-infected patients undergoing a renal biopsy. Renal outcomes in these patients were poor, although this may be due largely to most patients presenting with advanced disease.

[1]**See Editorial by Balow, p. 1632.**

Key words: human immunodeficiency virus, acquired immunodeficiency syndrome, lupus nephritis, renal biopsy.

Received for publication September 1, 2004
and in revised form October 14, 2004
Accepted for publication November 9, 2004

While the most common glomerular lesion associated with human immunodeficiency virus (HIV) infection is focal segmental glomerulosclerosis (FSGS), particularly the collapsing variant with marked associated tubulointerstitial changes [HIV-associated nephropathy (HIVAN)], immune complex-mediated glomerulonephritides have become increasingly recognized in HIV-positive patients [1–6]. The latter lesions include postinfectious glomerulonephritis, membranous nephropathy, IgA nephropathy, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and membranoproliferative glomerulonephritis (MPGN) [1–5], the latter most often in patients coinfected with hepatitis C virus [7, 8]. HIVAN, like primary FSGS and particularly collapsing FSGS not related to HIV, has a strong predilection for patients of black race [1, 2, 9–12]. By contrast, immune complex glomerulonephritis in HIV-infected patients has been reported mainly in white and Asian patients [2–4], although such lesions may occur in black patients as well, in some instances concomitantly with HIVAN [2].

One form of immune complex glomerulonephritis that has been described in the HIV-infected population is immune complex glomerulonephritis with "lupus-like" features, characterized by a "full house" pattern of immunoglobulin (IgG, IgA, and IgM) and complement (C3 and C1q) deposits within the glomeruli, often with large subendothelial deposits ("wire loops"). However, unlike HIV-infected patients with lupus nephritis [13–17], patients with lupus-like glomerulonephritis lack both serologic and clinical evidence of systemic lupus erythematosus (SLE). Nochy et al [2] reported that 22 (37%) of 60 French HIV-positive patients who underwent a renal biopsy had some form of immune complex

glomerulonephritis, with or without concurrent HIVAN, and ten of these 22 biopsies showed histologic, immunofluorescence, and electron microscopic features resembling diffuse proliferative lupus nephritis. Two of the biopsies showed concurrent HIVAN. Six of the ten patients were black and four were white, and none had positive lupus serologies, although these were not tested for in all patients [2]. Casanova et al [3] reported results from renal biopsies performed in 26 Italian HIV-positive patients, all white. Twenty of these patients had immune complex glomerulonephritis, none had HIVAN. Three of the 20 cases with immune complex deposits showed proliferative glomerulonephritis with lupus-like features, with subendothelial deposits in all three cases and hyaline thrombi and "wire loops" in two, although immunofluorescence studies were not done in one case. Antinuclear antibodies (ANA) were absent in those two cases where these were tested. In a series of consecutive renal biopsies from 136 predominantly African-American HIV-positive patients from New York City, D'Agati and Appel [1] found four cases of lupus-like glomerulonephritis.

Very limited information is presently available regarding treatment of and clinical outcomes in patients with lupus-like glomerulonephritis. Tabechian et al [18] recently reported a case of a 42-year-old HIV-positive white man who presented with nephrotic syndrome and renal insufficiency, who had two renal biopsies showing diffuse proliferative glomerulonephritis resembling World Health Organization (WHO) class IV lupus nephritis, but who had negative lupus serologies. His renal function remained stable while he received highly active antiretroviral therapy (HAART), but rapidly deteriorated to end-stage renal disease (ESRD) during an interval when HAART was discontinued and his HIV viral load increased.

In this paper, we present 14 cases of lupus-like glomerulonephritis in HIV-positive patients, emphasizing the morphologic features seen on renal biopsy as well as clinical presentations and outcomes of these patients. All 14 biopsies showed a "full house" pattern of glomerular immunoglobulin (IgG, IgA, and IgM) and complement (C3 and C1q) deposits by immunofluorescence, and each of the 12 biopsies examined by electron microscopy showed subendothelial and mesangial immune complex deposits, with subepithelial deposits in nine. Like true lupus nephritis, these cases of lupus-like glomerulonephritis showed a variety of histologic patterns, including diffuse proliferative and focal proliferative glomerulonephritis as well as membranous nephropathy without glomerular proliferative changes. However, renal outcomes were generally poor regardless of histologic pattern and treatment given, perhaps in large part because most of the patients presented with advanced disease with renal biopsies showing extensive chronic changes.

METHODS

Computerized records of the Department of Pathology, Johns Hopkins Hospital, were searched to identify all native renal biopsy specimens received from HIV-positive patients [with or without clinically evident acquired immunodeficiency syndrome (AIDS)] from January 1999 through December 2003. Excluding repeat biopsies, a total of 77 specimens were identified. We then examined the pathology reports for each of these specimens to identify those showing a "full house" pattern of glomerular immunoglobulin (IgG, IgA, and IgM) and complement (C3 and C1q) deposits by direct immunofluorescence studies performed on cryostat sections of unfixed tissue. Only cases showing granular staining in the glomerular capillary walls, mesangial areas, or both in all glomeruli present (excluding globally sclerotic glomeruli) with at least 1+ C1q staining on a 0 to 4+ scale of staining intensity were included; segmental, blotchy staining typical of hyalinosis lesions and nonspecific pseudolinear staining of glomerular capillary loops were not considered. For cases meeting these criteria, computerized patient records and clinical data received with the biopsy were examined to determine the results of tests for lupus serologies including ANA, antidouble-stranded DNA (anti-ds DNA), anti-Ro, anti-La, and anti-Smith (anti-Sm). Inclusion in this study was limited to patients with a negative ANA, or a weakly positive ANA (titer $\leq$1:80) with negative anti-ds DNA. A total of 14 patients met all of these pathologic and serologic criteria for inclusion in the study; none of these patients had a positive anti-ds DNA, anti-Ro, anti-La, or anti-Sm serologic test, although all of these were not tested for in every patient.

For these 14 cases, the computerized patient records and clinical data received with each of the 14 biopsy specimens were re-examined, and questionnaires requesting any information we sought (see below) that was not present in these records as well as follow-up clinical data were sent to the nephrologists caring for each patient. For each patient, the following information was recorded on spread sheets, identifying patients by only a study number (1 to 14): patient gender, race, and age, serum creatinine, 24-hour urine protein, the presence or absence of hematuria (microscopic and gross), and the presence or absence of nephrotic syndrome, the latter five parameters at the approximate time of the renal biopsy. Nephrotic syndrome was defined as proteinuria of at least 3.5 g/24 hours, with edema. We also recorded the presence or absence of hypertension (defined as systolic and diastolic blood pressures $\geq$130 mm Hg and $\geq$90 mm Hg, respectively, and/or treatment with antihypertensive medication), duration of HIV infection at the time of the biopsy and risk factors for HIV infection (e.g., intravenous drug abuse), lupus serologies (ANA, anti-ds DNA, anti-Ro, anti-La, and anti-Sm) and titers when positive, whether or not the

serum C3 level was below the reference range, and the presence or absence of hepatitis B surface antigen and hepatitis C. Finally, we recorded the medications received by each patient prior to and after the biopsy, whether each patient developed ESRD requiring dialysis or died and if so the number of months after the biopsy when these events occurred, and for those patients who had not developed ESRD the number of months after the biopsy of last follow-up, and the serum creatinine level at that time.

Examination of renal biopsies

Histologic slides from each biopsy, stained with hematoxylin and eosin, periodic acid-Schiff (PAS), silver methenamine, and Masson's trichrome stains, were examined by a renal pathologist (M.H.), blinded to the clinical data. For each biopsy, the following information was recorded on a second set of spread sheets, again using only the study numbers (1 to 14) as identifiers: (*1*) histologic type of glomerulonephritis (e.g., diffuse proliferative, focal proliferative, membranous), using the WHO classification for lupus nephritis [19] to define each histologic subtype (for diffuse proliferative glomerulonephritis, it was also noted if the lesion showed a membranoproliferative pattern, with diffuse endocapillary cell proliferation, hyperlobular glomeruli, and double contours of the glomerular basement membranes on PAS and silver stains); (*2*) presence or absence of crescents, and if present the fraction of glomeruli in which crescents were seen, not including globally sclerotic glomeruli; (*3*) presence or absence of glomerular "wire loops;" (*4*) the severity of tubulointerstitial scarring, estimated using the silver and trichrome stains as the percentage of the cortex, exclusive of glomeruli and arteries, occupied by sclerotic interstitium and atrophic tubules; and (*5*) presence of any concurrent lesions, including HIVAN (global or segmental collapse of the tuft in at least one glomerulus, with associated podocyte hyperplasia), thrombotic microangiopathy, or possible drug-induced interstitial nephritis, defined as focally heavy interstitial lymphocytic or lymphoplasmacytic infiltrates containing eosinophils [$\geq$5 per high power (400$\times$) field in one or more foci], located near the corticomedullary junction and/or in nonscarred areas of the cortex and/or outer medulla, and not directly adjacent to disrupted tubules containing proteinaceous casts.

Following this, the renal biopsy reports from these 14 cases were further reviewed and the following data recorded on the spread sheets containing the histopathologic findings: (*1*) the intensity (0 to 4+, in increments of 0.5+) of granular glomerular immunofluorescence staining for IgG, IgA, IgM, C3, C1q, kappa, and lambda, and whether this staining was in capillary walls, mesangium, or both; (*2*) if present, the location (e.g., tubular basement membranes, peritubular capillaries, focal or diffuse) and intensity of extraglomerular staining for any of the immune reactants; and (*3*) for those 12 cases in which electron microscopy was performed, the location (mesangial, subendothelial, subepithelial, or intramembranous) and relative amount of electron-dense deposits within glomeruli, the location of any extraglomerular deposits present, whether any of the deposits showed a specific (e.g., fibrillar, fingerprint-like) substructure, and if tubuloreticular inclusions (TRIs) were present in endothelial cell cytoplasm.

Electron micrographs from each biopsy were also reviewed and the findings compared with those described in the biopsy reports. In none of the 12 cases in which electron microscopy was performed were discrepancies found with respect to location of electron-dense deposits within or outside of glomeruli, presence or absence of substructure within deposits, or presence or absence of TRIs.

Data analysis

Clinical and pathologic data, with only the study numbers (1 to 14) as identifiers, were entered into an electronic database and the accuracy of data transcription was independently confirmed. Outlying values were identified using box plots and their accuracy checked against the original source data. Continuous data were summarized using means and standard deviations (SD), and compared using Mann-Whitney U tests. Categorical variables were compared using the chi-square test.

Renal survival was measured from the time of biopsy and was examined by time to event analysis using the Kaplan-Meier method. Univariate associations between clinical and pathologic parameters and renal survival were performed using Cox regression analysis. All study patients who died had ESRD requiring dialysis at the time of death, and as such censoring of these patients was not required. Analyses were performed using SPSS Base 7.5 (SPSS Inc., Chicago, IL, USA).

All study procedures were approved by the Institutional Review Board of Johns Hopkins Hospital.

RESULTS

A total of 77 native renal biopsies from HIV-positive patients, not including repeat biopsies, were evaluated at our center from January 1999 through December 2003. Primary renal biopsy diagnoses in all 77 patients, and within different racial groups, are summarized in Table 1. The most common diagnosis, accounting for 31 (40%) of the cases, was HIVAN, which was seen exclusively in African Americans. Twenty-six (34%) biopsies showed immune complex glomerulonephritis; 85% of these patients were also African Americans and six had concurrent HIVAN. Only one patient had lupus nephritis with serologic findings of SLE; this was a 10-year-old

Table 1. Primary renal biopsy diagnoses in 77 human immunodeficiency virus (HIV)-positive patients of different races

Diagnosis	Number (%) of cases in patients of indicated race			
	African American	White	Asian	All races
HIV-associated nephropathy	29 (43)	0	0	31 (40)[a]
Lupus-like glomerulonephritis	13 (19)	1 (14)	0	14 (18)
Focal segmental glomerulosclerosis, non-collapsing	11 (16)	2 (29)	0	13 (17)
Immune complex glomerulonephritis other than lupus-like glomerulonephritis[b]	9 (13)	2 (29)	1 (100)	12 (16)
Interstitial nephritis, drug-induced	2 (3)	2 (29)	0	4 (5)
Thrombotic microangiopathy	1 (1)	0	0	1 (1)
Amyloidosis, type AA	1 (1)	0	0	1 (1)
Hypertensive nephrosclerosis	1 (1)	0	0	1 (1)
All cases	67	7	1	77[a]
% Total patients of known race	89%	9%	1%	

[a]The race of two patients is not known.

[b]These diagnoses include IgA nephropathy (three cases), membranous nephropathy (two cases), resolving postinfectious glomerulonephritis (two cases), membranoproliferative glomerulonephritis type I (two cases), membranoproliferative glomerulonephritis type III (one case), lupus nephritis (one case), and mesangial proliferative glomerulonephritis with mesangial deposits of IgM and C3 (one case). Other than the single case of lupus nephritis, none of these biopsies showed a "full house" of glomerular immunoglobulin and complement deposits as defined in the **Methods** section.

Table 2. Demographic, clinical, and serologic features of patients with lupus-like glomerulonephritis

Age *years* (mean ± SD)	35.8 ± 9.2 (14)
Age *years*, range	10 to 47
Gender *male/female*	9/5
Race *African American/white*	13/1
Known duration of HIV *years* (mean ± SD)	10.3 ± 6.4 (12)
Known duration of HIV *years*, range	1 to 17
History of IVDA *fraction (%) of patients*	8/11 (73%)
Serum creatinine *mg/dL* (mean ± SD)	5.5 ± 4.3 (14)
Serum creatinine *mg/dL* range	0.7 to 16.0
Proteinuria *g/24 hours* (mean ± SD)	7.4 ± 7.3 (14)
Proteinuria *g/24 hours*, range	0.5 to 30.5
Nephrotic syndrome *fraction (%) of patients*	10/14 (71%)
Microscopic hematuria *fraction (%) of patients*	14/14 (100%)
Hypertension *fraction (%) of patients*	11/14 (79%)
Antinuclear antibodies *negative/weakly positive*	11/3
Hepatitis B surface antigen *fraction (%) positive*	1/10 (10%)
Hepatitis C *fraction (%) positive*	6/12 (50%)
Serum C3 *normal/decreased*	5/4

Numbers in parentheses without percent signs indicate numbers of patients. Levels of serum creatinine and proteinuria are at the approximate time of the renal biopsy. Nephrotic syndrome is defined as proteinuria ≥3.5 g/24 hours with edema; in eight of the ten patients meeting these criteria, serum albumin levels were known and ranged from 1.1 to 2.5 mg/dL. Weakly positive antinuclear antibodies are defined as a titer of ≤1:80. HIV is human immunodeficiency virus and IVDA is intravenous drug abuse.

boy with congenital HIV, and ANA and anti-ds DNA titers of 1:640 and 1:320, respectively. However, 14 (18% of total) biopsies met our criteria for showing lupus-like glomerulonephritis, namely showing a "full house" pattern of glomerular immunoglobulin (IgG, IgA, and IgM) and complement (C3 and C1q) deposits with at least 1+ staining intensity for C1q (0 to 4+ scale), with the patient having a negative ANA or a weakly positive (titer <1:80) ANA with negative anti-ds DNA. Demographic, clinical, and serologic features of these 14 patients are listed in Table 2. All but one of the patients were >28 years old at the time of the renal biopsy; the one remaining patient was a 10-year-old girl with neonatally acquired HIV. All but one patient were African Americans, and in eight of 12 cases where this information was available patients were known to be HIV-positive for at least 10 years prior to the biopsy. The majority of patients presented with severe renal insufficiency (serum creatinine >3.0 mg/dL in nine of 14), heavy proteinuria (24-hour urine protein >5.0 g in 10 of 14) and the nephrotic syndrome, and hypertension; all had microscopic hematuria, although none had gross hematuria. ANA was negative in 11 of the 14 patients; six of these patients also had testing done for anti-ds DNA and in each case this was negative as well. Three patients had weakly positive ANA (1:40 titer in one patient and 1:80 in two) with negative anti-ds DNA and anti-Sm; in two of these patients where tests were done anti-Ro and anti-La were also negative. Serum C3 was low in four of nine patients in which this was examined.

Six of 12 patients tested had positive hepatitis C serology (Table 2), although none had documented cryoglobulinemia. As hepatitis C and HIV coinfection has been found to be associated with immune complex-mediated glomerulonephritis [7, 8], we compared clinical and demographic data in the six hepatitis C–positive patients with that in the six patients known to be hepatitis C–negative (Table 3). Although there were some minor differences among these two groups of patients, including a higher mean level of proteinuria in the hepatitis C–positive cohort, none of these differences were statistically significant.

Histologic findings from the 14 renal biopsies are summarized in Table 4, with examples shown in Figure 1. These histologic data are also subclassified according to the patients' hepatitis C status. Seven of the biopsies showed diffuse proliferative glomerulonephritis with endocapillary cell proliferation in the majority of glomeruli, exclusive of globally sclerotic glomeruli. In two of these biopsies, including that represented in Figure 1A to C, the glomerulonephritis had a pattern resembling MPGN, type I, with diffusely hypercellular and hyperlobular glomeruli and double contours of the glomerular basement membranes on silver stain and on electron microscopy, with multiple mesangial and subendothelial immune complex deposits. One of the biopsies with this pattern of glomerulonephritis (Fig. 1A to C) was from a hepatitis C–positive patient, while the other was from a hepatitis C–negative patient. One additional biopsy with diffuse proliferative glomerulonephritis (Fig. 1D to F)

Table 3. Demographic, clinical, and serologic features of patients with lupus-like glomerulonephritis, subclassified according to hepatitis C serology

	Hepatitis C–positive	Hepatitis C–negative
Age *years* (mean ± SD)	33.3 ± 11.8 (6)	36.8 ± 7.6 (6)
Age *years*, range	10 to 41	28 to 47
Gender *male/female*	4/2	4/2
Race *African American/white*	6/0	5/1
Known duration of HIV *years* (mean ± SD)	11.7 ± 5.8 (6)	9.4 ± 7.8 (5)
Known duration of HIV *years*, range	1 to 17	1 to 14
History of IVDA *fraction (%) of patients*	4/5 (80%)	3/5 (60%)
Serum creatinine *mg/dL* (mean ± SD)	4.0 ± 2.7 (6)	5.7 ± 3.7 (6)
Serum creatinine *mg/dL*, range	0.7 to 7.8	1.8 to 10.1
Proteinuria *g/24 hours* (mean ± SD)	6.4 ± 3.5 (6)	4.4 ± 3.1 (6)
Proteinuria *g/24 hours*, range	0.5 to 9.5	1.2 to 9.0
Nephrotic syndrome *fraction (%) of patients*	5/6 (83%)	3/6 (50%)
Hypertension *fraction (%) of patients*	5/6 (83%)	4/6 (67%)
Antinuclear antibodies *negative/weakly positive*	5/1	5/1
Hepatitis B surface antigen *fraction (%) positive*	1/4 (25%)	0/6 (0%)
Serum C3 *normal/decreased*	3/1	2/2

Numbers in parentheses without percentages indicate numbers of patients. Levels of serum creatinine and proteinuria are at the approximate time of the renal biopsy. Nephrotic syndrome is defined as proteinuria ≥3.5 g/24 hours with edema; in eight of the ten patients meeting these criteria, serum albumin levels were known and ranged from 1.1 to 2.5 mg/dL. Weakly positive antinuclear antibodies are defined as a titer of ≤1:80. None of the parameters listed were significantly different in hepatitis C–positive and hepatitis C–negative patients ($P > 0.30$ in all instances). HIV is human immunodeficiency virus and IVDA is intravenous drug abuse.

showed crescents in 50% of the glomeruli present, with focal and segmental "wire loops," corresponding thick capillary wall deposits on immunofluorescence and large subendothelial deposits on electron microscopy. Six biopsies showed focal proliferative glomerulonephritis with endocapillary proliferation in <50% of glomeruli. Three of these biopsies, including that shown in Figure 1G to I, showed concurrent HIVAN, and each of the three corresponding patients presented with nephrotic syndrome and proteinuria of >6.0 g/24 hours. One biopsy (Fig. 1J to L) showed membranous nephropathy resembling membranous (WHO class V) lupus nephritis. Glomeruli were normocellular, although immunofluorescence showed mesangial as well as glomerular capillary wall staining and electron microscopy showed mesangial and rare subendothelial deposits (the latter not present in Fig. 1L) in addition to more numerous subepithelial and intramembranous deposits. There was a trend toward a difference in the distribution of histologic patterns of glomerulonephritis between hepatitis C–positive and hepatitis C–negative patients (Table 4), although this did not reach statistical significance in this relatively small sample of cases ($P = 0.07$).

A prominent feature of most of these biopsies was the presence of moderate or severe tubular atrophy and interstitial fibrosis (Table 4). Five biopsies, all but one from patients without concurrent HIVAN, showed focally severe interstitial inflammation not limited to scarred areas of the insterstitum, with focal clusters of eosinophils, suggestive of possible drug-induced interstitial nephritis. None of these five patients were on HAART at the time of the biopsy and none of the biopsies showed granulomatous inflammation, multinucleated giant cells, or crystals of the type described in some patients taking indinavir [20]. Two biopsies, including that shown in Figure 1A, showed focal changes of thrombotic microangiopathy, with very focal fibrin thrombi and red blood cell fragments within glomeruli and preglomerular arterioles.

Immunofluorescence and electron microscopy findings from the 14 biopsies are summarized in Tables 5 and 6, respectively. The majority of biopsies showed at least moderately intense (>1+) staining for all immunoglobulins and complement components tested except for IgA, which was only mildly positive (≤1+) in all but three biopsies. No significant differences were noted between hepatitis C–positive and hepatitis C–negative patients with respect to the mean intensity of staining for any of the immune reactants listed in Table 5 (data not shown). None of the biopsies showed staining limited to the mesangial areas for all immunoglobulins and complement components. Likewise, all 12 biopsies examined by electron microscopy showed mesangial and subendothelial electron-dense deposits, although the latter were rare in the one case of membranous nephropathy. The majority of cases showed subepithelial deposits as well. One biopsy (Fig. 1H) showed focal immune complex deposits within tubular basement membranes by both immunofluorescence (IgG, C3, and C1q) and electron microscopy. All 12 biopsies on which electron microscopy was performed showed TRIs within glomerular endothelial cells.

Outcomes

Follow-up data were available for all of the 14 patients. Two of the patients were dialysis-dependent at the time of the biopsy and eight others subsequently developed ESRD, all within 1 year of the biopsy. Three of the ten patients who developed ESRD received HAART and three received corticosteroids following the biopsy. Four patients died from 3 to 12 months following the biopsy, and all had ESRD at the time of death. Four patients are alive with functioning kidneys. One, diagnosed as being HIV-positive during the year prior to the biopsy and having no history of opportunistic infections, had membranous nephropathy with moderate tubulointerstitial

Table 4. Histologic findings in renal biopsies of patients with lupus-like glomerulonephritis

	All cases (14)	Hepatitis C–positive (6)	Hepatitis C–negative (6)
Histologic pattern of glomerulonephritis *number (%) of cases*			
Diffuse proliferative	7 (50%)	4 (67%)	1 (17%)[a]
Focal proliferative	6 (43%)	1 (17%)	5 (83%)
Membranous	1 (7%)	1 (17%)	0
Tubulointerstitial scarring *number (%) of cases*			
Minimal (estimated <10% of cortex present)	0	0	0
Mild (estimated 10% to 24%)	2 (14%)	1 (17%)	1 (17%)
Moderate (estimated 25% to 49%)	5 (36%)	2 (33%)	1 (17%)
Severe (estimated ≥50%)	7 (50%)	3 (50%)	4 (67%)
Crescents (one or more) *number (%) of cases*	6 (43%)	2 (33%)	3 (50%)
Crescents in ≥50% of glomeruli *number (%) of cases*	1 (7%)	1 (17%)	0
Glomerular "wire loops" *number (%) of cases*	1 (7%)	1 (17%)	0
Concurrent HIVAN *number (%) of cases*	3 (21%)	1 (17%)	2 (33%)
Concurrent thrombotic microangiopathy *number (%) of cases*	2 (14%)	1 (17%)	1 (17%)
Possible concurrent int. nephritis *number (%) of cases*	5 (36%)	2 (33%)	2 (33%)

[a] $P = 0.07$ for the difference in distribution of histologic patterns of glomerulonephritis between hepatitis C–positive and hepatitis C–negative patients by chi-square test. All other parameters were not significantly different ($P > 0.30$) between hepatitis C–positive and hepatitis C–negative patients. HIVAN is human immunodeficiency virus (HIV)-associated nephropathy.

scarring (according to the criteria in Table 4), an initial serum creatinine of 1.4 mg/dL, nephrotic syndrome with proteinuria of 9.5 g/24 hours, and mild hypertension. He has been treated only with angiotensin-converting enzyme (ACE) inhibitors and 10 months following the biopsy continues to have nephrotic range proteinuria and mild edema, with a serum creatinine of 1.7 mg/dL and normal blood pressure. Another, also diagnosed as HIV-positive within a year prior to the biopsy, had diffuse proliferative glomerulonephritis with rare crescents, severe tubulointerstitial scarring, probable drug-induced interstitial nephritis (she was taking ibuprofen), and an initial serum creatinine of 3.3 mg/dL. She was treated with prednisone for 3 months and discontinued the ibuprofen; 17 months following the biopsy her serum creatinine is 2.1 mg/dL. The two remaining patients, both with long-standing HIV disease and AIDS, had biopsies showing focal proliferative glomerulonephritis (with rare crescents in one) with mild or moderate tubulointerstitial scarring. Their initial serum creatinine levels were 1.8 and 2.1 mg/dL, respectively. Both patients have been maintained on HAART; 43 and 42 months postbiopsy, respectively, their serum creatinine levels are 1.5 and 1.3 mg/dL. Notably, other than the patient with membranous nephropathy, those patients who did not develop ESRD had proteinuria below the nephrotic range (1.2, 1.3, and 3.0 g/24 hours), and none had edema at the time of biopsy. By contrast, all but one of the patients who developed ESRD had proteinuria of >5 g/24 hours and the nephrotic syndrome, including the three patients whose biopsies showed concurrent HIVAN.

Figure 2 illustrates renal survival for the cohort of 14 patients, based on Kaplan-Meier analysis, and Table 7 lists univariate associations between a number of clinical and morphologic parameters and renal survival. Of the parameters listed in Table 7, only the serum creatinine at the time of biopsy showed a significant association with renal survival. However, if only cases of focal and diffuse proliferative glomerulonephritis are considered (i.e., the single case of membranous nephropathy is excluded), nephrotic range proteinuria and increasing severity of tubulointerstitial scarring (see **Methods** section) (see alsoTable 7 legend) each showed a borderline significant ($P = 0.04$ and 0.05, respectively) negative association with renal survival.

DISCUSSION

Lupus-like glomerulonephritis, defined by the presence of a "full house" of glomerular immunoglobulin and complement deposits on immunofluorescence in the absence of serologic evidence of SLE, was found in 14 of 77 (18%) native renal biopsies from HIV-positive patients processed at our center from January 1999 through December 2003, making this second to HIVAN (present in 37 biopsies, six with concurrent immune complex glomerulonephritis) among the most common glomerular lesions in HIV-positive patients undergoing a renal biopsy during this 5-year period. Our definition of lupus-like glomerulonephritis is somewhat less limited than has been used in some previous studies [2, 3], in that we did not restrict this diagnosis to cases showing "wire loops" or diffuse proliferative glomerulonephritis with prominent subendothelial deposits on electron microscopy. This was done because lupus nephritis itself may present with a variety of histologic patterns [19], but with immune complexes containing IgG, IgA, IgM, C3, and C1q being common in each form, even "pure" membranous nephropathy [21]. Our serologic criteria were designed to prevent the inclusion of cases of true lupus nephritis, which may occur in HIV-positive patients [13–17]. While it is not uncommon for HIV-positive patients without SLE to have circulating ANA, titers in these patients are rarely >1:160, and anti-ds DNA is absent [22].

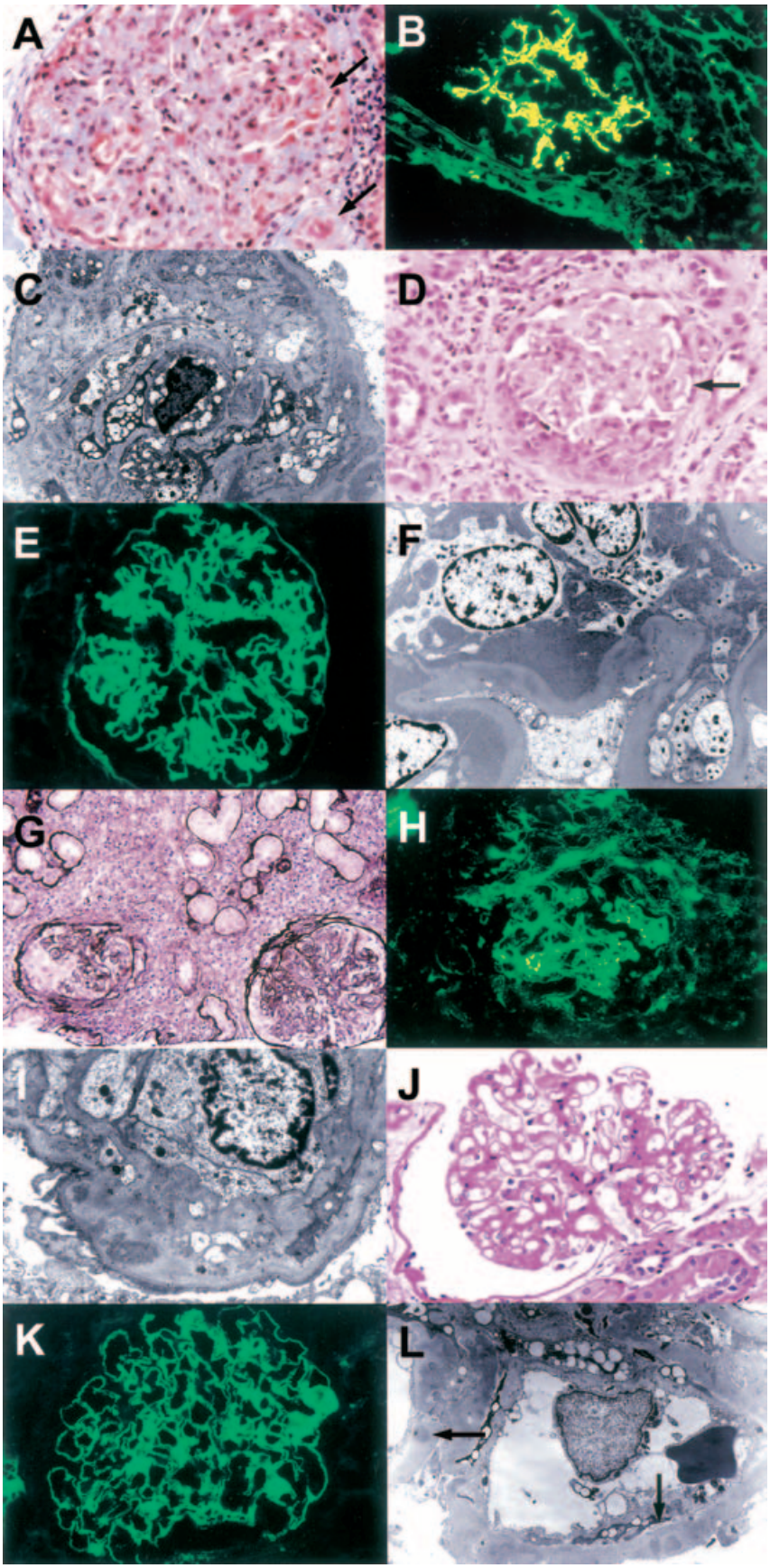

Fig. 1. Light microscopic, immunofluorescence, and electron microscopic features of four renal biopsies showing lupus-like glomerulonephritis. (*A* to *C*) Diffuse proliferative glomerulonephritis with a pattern resembling membranoproliferative glomerulonephritis, type I. The glomerulus (A) is enlarged with global mesangial and endocapillary hypercellularity, and appears mildly hyperlobular. There is partial occlusion of a preglomerular arteriole by thrombus and rare red blood cell fragments within the glomerular tuft (arrows), indicative of a thrombotic microangiopathy. Immunofluorescence (B) shows strong (3+ on a 0 to 4+ scale) mesangial and segmental capillary wall staining for C3, and electron microscopy (C) shows duplication of the glomerular basement membrane (GBM) with subendothelial and mesangial electron-dense deposits. (*D* to *F*) Diffuse proliferative glomerulonephritis with crescents and "wire loops." The glomerulus (D) shows a segmental cellular crescent; crescents were seen in 50% of glomeruli on this biopsy. The arrow indicates a severely thickened capillary loop ("wire loop"). Immunofluorescence for IgG (E) shows moderately intense (2+) staining in mesangial areas and capillary walls, with some of the capillary wall staining appearing thick, possibly corresponding to "wire loops." Electron microscopy (F) shows large mesangial and subendothelial (bottom left) deposits. (*G* to *I*) Focal proliferative glomerulonephritis with superimposed human immunodeficiency virus (HIV)-associated nephropathy (HIVAN). (G) The glomerulus at right shows segmental endocapillary hypercellularity (particularly in the upper left quadrant of the glomerulus), while that at left shows segmental collapse of the tuft with associated swollen, hyperplastic podocytes (left portion of glomerulus). Immunofluorescence for C1q (H) shows mildly to moderately intense (1 to 2+) glomerular staining, mainly in capillary walls, and weaker, finely granular staining in some tubular basement membranes. Electron microscopy (I) shows subendothelial deposits and duplication of the GBM. (*J* to *L*) Membranous nephropathy. The representative glomerulus in (J) is normocellular with a mild increase in mesangial matrix. Immunofluorescence for IgA (K) shows 2+, confluent granular staining in the glomerular capillary walls and mesangial areas. Electron microscopy (L) shows thickening of the GBM with subepithelial and intramembranous deposits (arrows), with mesangial deposits at the very top of the electron micrograph. This biopsy showed a moderate number of mesangial deposits and rare subendothelial deposits, the latter not shown in this panel. (A) Masson's trichrome stain (original magnification ×400). (B) Fluorescein isothiocyanate (FITC)-conjugated antihuman C3 (×400). (C) Uranyl acetate and lead citrate stain (×3000). (D) Hematoxylin and eosin (×400). (E) FITC antihuman IgG (×400). (F) Uranyl acetate and lead citrate (×5000). (G) Silver methenamine (×200). (H) FITC antihuman C1q (×400). (I) Uranyl acetate and lead citrate (×3800). (J) Periodic acid-Schiff (PAS) (×400). (K) FITC antihuman IgA (×400). (L) Uranyl acetate and lead citrate (×4000).

Table 5. Immunofluorescence findings in renal biopsies of patients with lupus-like glomerulonephritis

Immune reactant	Staining intensity (mean ± SD)[a]	Number (%) >1+	Capillary wall + mesangial	Mesangial only
IgG	2.0 ± 0.8	12 (86%)	10 (71%)[b]	4 (29%)
IgA	1.1 ± 0.4	3 (21%)	9 (64%)[b]	5 (36%)
IgM	2.1 ± 0.6	13 (93%)	13 (93%)	1 (7%)
C3	2.3 ± 0.8	12 (86%)	12 (86%)	2 (14%)
C1q	1.4 ± 0.3	9 (64%)	10 (71%)[b]	4 (29%)
Kappa	1.6 ± 0.5	9 (64%)	14 (100%)[b]	0
Lambda	1.3 ± 0.4	6 (43%)	14 (100%)[b]	0

[a]Staining for each immune reactant was graded on a 0 to 4+ scale, in increments of 0.5+. In addition to the glomerular staining noted in this table, one biopsy showed focal, fine granular tubular basement membrane staining for IgG, C3, and C1q (all 0.5+).

[b]In one case, staining was limited to the capillary walls with minimal mesangial staining.

Table 6. Electron microscopic findings in renal biopsies of patients with lupus-like glomerulonephritis

Location of deposits	Number (%) of cases
Mesangial and subendothelial	3 (25%)
Mesangial, subendothelial, and subepithelial	4 (33%)
Mesangial, subendothelial, subepithelial, and intramembranous	5 (42%)
Tubular basement membranes (in addition to glomeruli)	1 (8%)
Tubuloreticular inclusions	12 (100%)

Electron microscopy was not performed in two cases as tissue processed for electron microscopy did not contain glomeruli. None of the deposits present had a specific substructure. The one biopsy that showed very focal, small tubular basement membrane deposits by electron microscopy corresponded to that showing focal tubular basement membrane staining by immunofluorescence (see also Table 5 and Figure 1H).

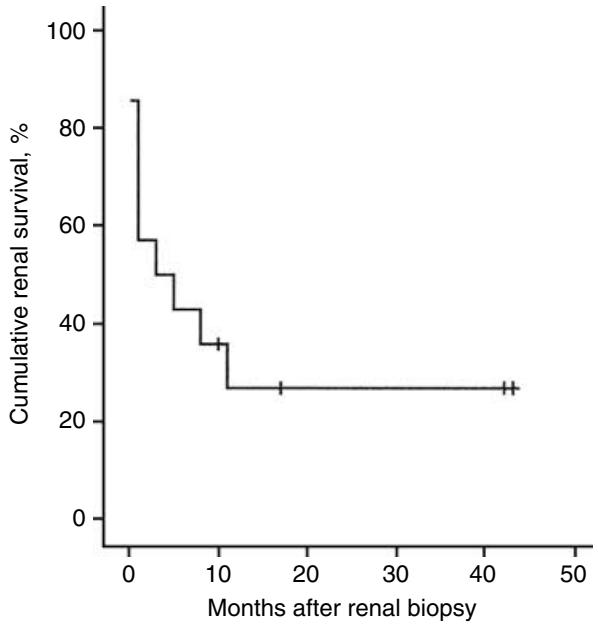

Fig. 2. Kaplan-Meier plot of renal survival from the time of the renal biopsy for all 14 cases of lupus-like glomerulonephritis. Vertical hash marks each indicate the end of follow-up for a patient who has not developed end-stage renal disease (ESRD).

It is of interest that 13 of our 14 patients with lupus-like glomerulonephritis are African Americans. This would appear consistent with the racial composition of the HIV-positive population of the Baltimore metropolitan area from which most of our HIV/AIDS patients are derived, and is similar to the racial composition of all HIV-positive patients undergoing a native renal biopsy at our center from 1999 to 2003 (89% black among those 75 patients whose race is known). While European studies have found that HIVAN is mainly limited to black patients and that most cases of glomerular disease in white HIV-infected patients are immune complex-mediated [2, 3], it would appear from the present study and that of Nochy et al [2], which showed lupus-like glomerulonephritis in fairly similar fractions of black and white HIV-positive patients undergoing a renal biopsy, that lupus-like glomerulonephritis does not have a strong predilection for individuals of either race.

Six of our patients were known to be hepatitis C–positive, which raises the question of whether the lupus-like glomerulonephritis in these patients may be secondary to hepatitis C rather than HIV. Four of the six hepatitis C–positive patients had diffuse proliferative glomerulonephritis, one had focal proliferative glomerulonephritis and one had membranous nephropathy; one of the diffuse proliferative lesions had a MPGN-like pattern. The histology of this latter case in particular, together with the reduced serum levels of C3 and C4 in this patient, suggest a possible hepatitis C–related glomerulonephritis. Arguing against this, however, is the fact that none of the 16 cases of MPGN in patients coinfected with hepatitis C and HIV reported by Cheng et al [7] and Stokes et al [8] showed a "full house" of glomerular immunoglobulin and complement deposits with more than equivocal or trace staining for all immune reactants. Furthermore, of the 20 hepatitis C–positive patients (17 HIV-negative, three HIV-positive) diagnosed with noncryoglobulinemic MPGN type I or type III at our center from 1999 through 2003, only two had a "full house" of glomerular immunoglobulin and complement deposits with more than equivocal or trace staining for all immune reactants including C1q. By contrast, such staining was observed in each of our six cases of lupus-like glomerulonephritis in HIV- and hepatitis C–positive patients.

There is presently little information known about the etiology of lupus-like glomerulonephritis, its treatment, or its long-term outcome. HIV infection is associated with polyclonal B cell activation, and circulating immune complexes are commonly seen in HIV-infected patients [23, 24]. It is possible that deposition of such immune complexes within glomeruli could play a pathogenic role in mediating lupus-like glomerulonephritis and other forms

Table 7. Univariate associations of clinical and morphologic parameters with renal survival

Parameters	Hazard ratio	95% CI	*P* value
Age *per year*	1.01	0.94, 1.08	0.80
Gender			
Female	Reference		
Male	1.01	0.28, 3.62	0.98
Duration of human immunodeficiency virus *per year*	1.14	0.92, 1.41	0.24
Serum creatinine *mg/dL* (all cases)	1.32	1.09, 1.59	**0.005**
Serum creatinine *mg/dL* (proliferative glomerulonephritis only)	1.30	1.07, 1.57	**0.007**
Proteinuria (all cases)			
<3.5 g/24 hours	Reference		
≥3.5 g/24 hours	7.8	0.94, 65.3	0.06
Proteinuria (proliferative glomerulonephritis only)			
<3.5 g/24 hours	Reference		
≥3.5 g/24 hours	9.6	1.16, 79.3	**0.04**
Hepatitis C serology			
Negative	Reference		
Positive	1.44	0.34, 6.17	0.62
Pattern of glomerulonephritis			
Focal proliferative	Reference		
Diffuse proliferative	1.25	0.35, 4.50	0.73
Cellular/fibrocellular crescents			
None	Reference		
≥1	0.89	0.25, 3.18	0.86
Tubulointerstitial scarring (per 10%)			
All cases	1.69	0.97, 2.90	0.07
Proliferative glomerulonephritis only	1.71	1.00, 2.94	0.05

Analyses were performed using the Cox regression model. A hazard ratio of >1.00 indicates an association with poorer renal survival; associations that are statistically significant ($P < 0.05$) have their *P* values in boldface type. For tubulointerstitial scarring, the hazard ratio shown is for each 10% increase in the estimated fraction of renal cortex, exclusive of glomeruli and arteries, that is occupied by sclerotic interstitium and atrophic tubules (see the **Methods** section).

of glomerulonephritis, such as IgA nephropathy, which occur in HIV-infected patients. In support of this hypothesis, Kimmel et al [6] described four HIV-positive patients with immune complex glomerulonephritis, which in one case showed a "full house" pattern of immunoglobulin and complement deposits within glomeruli by immunofluorescence. Each of these four patients had one or more types of circulating immune complexes comprised of IgG, IgA, and/or IgM antibodies and HIV antigens (p24 and gp120), and both antibodies and HIV antigens were eluted from the renal biopsies of these patients. At least one of the antibodies identified, an IgG anti-p24, was found to be complement-fixing [6].

Tabechian et al [18] reported a case of a 42-year-old HIV-positive white man presenting with nephrotic syndrome, renal insufficiency, and negative lupus serologies, who had two renal biopsies showing diffuse proliferative glomerulonephritis resembling WHO class IV lupus nephritis. His renal function remained stable while he received HAART, but rapidly deteriorated to ESRD during an interval when HAART was discontinued and his HIV viral load increased. There are additional case reports of HIV-positive patients with immune complex-mediated glomerular diseases showing reduction of proteinuria following treatment with multidrug antiretroviral regimens [25, 26], although a recent multicenter study failed to show a significant effect of antiretroviral therapy on renal survival in HIV-positive patients with a variety of glomerular lesions other than HIVAN, most immune complex-mediated [27]. Five of our patients were treated with HAART and two showed an improvement in renal function that was stable 42 and 43 months after the biopsy, respectively. The other three patients developed ESRD within a year of the biopsy, although two of these patients had very severe renal insufficiency (serum creatinine >7 mg/dL) and nephrotic syndrome at the time of their biopsies. Four additional patients were treated with corticosteroids, which have been reported to be efficacious in treating some cases of HIVAN [28] and a case of membranous nephropathy in a patient with AIDS [29]. One of these patients showed improved renal function 17 months postbiopsy, although this may be due primarily to treatment of interstitial nephritis due to ibuprofen, which was discontinued after the biopsy. The remaining three patients developed ESRD within 3 months of the biopsy; each had severe renal insufficiency (serum creatinine >3 mg/dL) and nephrotic sydrome at the time of biopsy.

Renal survival in our cohort of patients with lupus-like glomerulonephritis was generally poor, and not dissimilar to that in patients with HIV and hepatitis C–associated MPGN or HIVAN whose renal biopsies showed at least moderate interstitial fibrosis [7, 12]. In patients with collapsing FSGS, including HIVAN, renal outcomes were found to be significantly better in patients whose renal biopsies showed <20% interstitial fibrosis than in those whose biopsies showed >20% interstitial fibrosis [12]. Similar findings have been reported for non-HIV–infected patients with immune complex-mediated forms of glomerulonephritis such as lupus nephritis [30, 31] and IgA nephropathy [32–34]. By univariate analysis, and considering only those 13 patients with focal or diffuse proliferative glomerulonephritis, we found a borderline significant negative correlation between the severity of chronic tubulointerstitial change and renal survival in our patients with lupus-like glomerulonephritis, although it was not possible to perform a multivariate analysis of factors affecting renal survival because of the small patient sample. Likewise, excluding the one patient with membranous nephropathy, we found that nephrotic range proteinuria was significantly and negatively correlated with renal survival. This is not surprising, noting that heavy proteinuria is well-documented as a negative prognostic indicator for renal survival in other glomerular diseases [31–37].

CONCLUSION

Lupus-like glomerulonephritis is not an uncommon form of glomerular disease in HIV-infected patients undergoing a renal biopsy. This form of glomerulonephritis may occur in African American or white individuals, alone or concurrently with HIVAN. The clinical presentation is most often nephrotic syndrome and renal insufficiency, the latter often severe. Renal survival among our patients with lupus-like glomerulonephritis was poor, with ten of 14 patients developing ESRD, each within 1 year of his or her diagnostic renal biopsy. However, whether this is truly representative of the complete spectrum of patients with lupus-like glomerulonephritis, and whether this form of glomerulonephritis is responsive to treatment with HAART and/or corticiosteroids, remain to be determined as most of our patients already had advanced disease at the time of their renal biopsies.

Reprint requests to Mark Haas, M.D., Ph.D., Department of Pathology, Johns Hopkins University School of Medicine, 712 Pathology Bldg., 600 N. Wolfe St., Baltimore, MD 21287.
E-mail: mhaas@jhmi.edu

REFERENCES

1. D'Agati V, Appel GB: Renal pathology of human immunodeficiency virus infection. *Semin Nephrol* 18:406–421, 1998
2. Nochy D, Glotz D, Dosquet P, *et al*: Renal disease associated with HIV infection: A multicentric study of 60 patients from Paris hospitals. *Nephrol Dial Transplant* 8:11–19, 1993
3. Casanova S, Mazzucco G, Barbiano di Belgiojoso G, *et al*: Pattern of glomerular involvement in human immunodeficiency virus-infected patients: an Italian study. *Am J Kidney Dis* 26:446–453, 1995
4. Praditpornsilpa K, Napathorn S, Yenrudi S, *et al*: Renal pathology and HIV infection in Thailand. *Am J Kidney Dis* 33:282–286, 1999
5. Haas M, Rajaraman S, Ahuja T, *et al*: Fibrillary/immunotactoid glomerulonephritis in HIV-positive patients: A report of 3 cases. *Nephrol Dial Transplant* 15:1679–1683, 2000
6. Kimmel P, Phillips TM, Ferreira-Centeno A, *et al*: HIV-associated immune-mediated renal disease. *Kidney Int* 44:1327–1340, 1993
7. Cheng J-T, Anderson HL Jr., Markowitz GS, *et al*: Hepatitis C virus-associated glomerular disease in patients with human immunodeficiency virus coinfection. *J Am Soc Nephrol* 10:1566–1574, 1999
8. Stokes MB, Chawla H, Brody RI, *et al*: Immune complex glomerulonephritis in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Am J Kidney Dis* 29:514–525, 1997
9. Bakir AA, Bazilinski NG, Rhee HL, *et al*: Focal segmental glomerulosclerosis: A common entity in nephrotic black adults. *Arch Intern Med* 149:1802–1804, 1989
10. Bourgoignie JJ, Ortiz-Interian C, Green DF, Roth D: Race, a cofactor in HIV-1-associated nephropathy. *Transplant Proc* 21:3899–3901, 1989
11. Detwiler RK, Falk RJ, Hogan SL, Jennette JC: Collapsing glomerulopathy: A clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int* 45:1416–1425, 1994
12. Laurinavicius A, Hurwitz S, Rennke HG: Collapsing glomerulopathy in HIV and non-HIV patients: A clinicopathologic and follow-up study. *Kidney Int* 56:2203–2213, 1999
13. Strauss J, Abitbol C, Zilleruelo G, *et al*: Renal disease in children with the acquired immunodeficiency syndrome. *N Engl J Med* 321:625–630, 1989
14. D'Agati V, Seigle R: Coexistence of AIDS and lupus nephritis: A case report. *Am J Nephrol* 10:243–247, 1990
15. Contreras G, Green DF, Pardo V, *et al*: Systemic lupus erythematosus in two adults with human immunodeficiency virus infection. *Am J Kidney Dis* 28:292–295, 1996
16. Alonzo CM, Lozada CJ: Effects of IV cyclophosphamide on HIV viral replication in a patient with systemic lupus erythematosus. *Clin Exp Rheumatol* 18:510–512, 2000
17. Chang BG, Markowitz GS, Seshan SV, *et al*: Renal manifestations of concurrent systemic lupus erythematosus and HIV infection. *Am J Kidney Dis* 33:441–449, 1999
18. Tabechian D, Pattanaik D, Suresh U, *et al*: Lupus-like nephritis in an HIV-positive patient: Report of a case and review of the literature. *Clin Nephrol* 60:187–194, 2003
19. Weening JJ, D'Agati VD, Schwartz MM, *et al*: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 65:521–530, 2004
20. Jaradat M, Phillips C, Yum M-N, *et al*: Acute tubulointerstitial nephritis attributable to indinavir therapy. *Am J Kidney Dis* 35:E16–E20, 2000
21. Haas M: IgG subclass deposits in glomeruli of lupus and non-lupus membranous nephropathies. *Am J Kidney Dis* 23:358–364, 1994
22. Kopelman RG, Zolla-Pazner S: Association of human immunodeficiency virus infection and autoimmune phenomena. *Am J Med* 84:82–88, 1988
23. Lane HC, Masur H, Edgar LC, *et al*: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 309:453–458, 1983
24. McDougal JS, Hubbard M, Nicholson JKA, *et al*: Immune complexes in the acquired immunodeficiency syndrome (AIDS): Relationship to disease manifestation, risk group, and immunologic defect. *J Clin Immunol* 5:130–138, 1985
25. Dellow E, Unwin R, Miller R, *et al*: Protease inhibitor therapy for HIV infection: The effect on HIV-associated nephrotic syndrome. *Nephrol Dial Transplant* 14:744–747, 1999
26. Alarcon-Zurita A, Salas A, Anton E, *et al*: Membranous glomerulonephritis with nephrotic syndrome in a HIV positive patient—Remarkable remission with triple therapy. *Nephrol Dial Transplant* 15:1097–1098, 2000
27. Szczech LA, Gupta SK, Habash R, *et al*: The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* 66:1145–1152, 2004
28. Briggs WA, Tanawattanacharoen S, Choi MJ, *et al*: Clinicopathologic correlates of prednisone treatment of human immunodeficiency virus-associated nephropathy. *Am J Kidney Dis* 28:618–621, 1996
29. Mattana J, Siegal FP, Schwarzwald E, *et al*: AIDS-associated membranous nephropathy with advanced renal failure: response to prednisone. *Am J Kidney Dis* 30:116–119, 1997
30. Austin HA III, Boumpas DT, Vaughan EM, Balow JE: Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int* 45:544–550, 1994
31. Esdaile JM, Levinton C, Federgreen W, *et al*: The clinical and renal biopsy predictors of long-term outcome in lupus nephritis: a study of 87 patients and review of the literature. *Q J Med* 72:779–833, 1989
32. Haas M: Histologic subclassification of IgA nephropathy: A clinicopathologic study of 244 cases. *Am J Kidney Dis* 29:829–842, 1997
33. D'Amico G: Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. *Am J Kidney Dis* 36:227–237, 2000
34. Daniel L, Saingra Y, Giorgi R, *et al*: Tubular lesions determine prognosis of IgA nephropathy. *Am J Kidney Dis* 35:13–20, 2000
35. Bartosik LP, Lajoie G, Sugar L, Cattran DC: Predicting progression in IgA nephropathy. *Am J Kidney Dis* 38:728–735, 2001
36. Reichert LJM, Koene RAP, Wetzels JFM: Prognostic factors in idiopathic membranous nephropathy. *Am J Kidney Dis* 31:1–11, 1998
37. Rydel JJ, Korbet SM, Borok RZ, Schwartz MM: Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. *Am J Kidney Dis* 25:534–542, 1995