Hepatitis C Virus-Associated Glomerular Disease in Patients with Human Immunodeficiency Virus Coinfection

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Abstract. Chronic infection with hepatitis C virus (HCV) has been linked to the development of glomerular disease. HCV infection is highly prevalent among intravenous drug users, a population that is also at risk for HIV coinfection. This study reports the clinical-pathologic features and outcome of HCV-associated glomerular disease (HCV-GD) in 14 patients with HIV coinfection. All were intravenous drug users and all but one were African-Americans. Renal presentations included renal insufficiency, microscopic hematuria with active urine sediment, hypertension, and nephrotic syndrome or nephrotic-range proteinuria without hypercholesterolemia. Hypocomplementemia and cryoglobulinemia were present in 46 and 33% of patients, respectively. The predominant renal biopsy findings were membranoproliferative glomerulonephritis type 1 or type 3 (Burkholder subtype) in 79% of patients and membranous glomerulopathy with atypical features in 21% (including overlap with collapsing glomerulopathy in one patient). The clinical course was characterized by rapid progression to renal failure requiring dialysis. The overall morbidity and mortality were high with median time of 5.8 mo to dialysis or death. Although most patients died in renal failure, cause of death was primarily attributable to long-term immunosuppression and advanced AIDS. Patients with AIDS had shorter survival than those without (median survival time of 6.1 mo *versus* 45.9 mo, log-rank test $P = 0.02$). Only two patients were alive with stable renal function at follow-up of 28.5 mo. In patients with HCV-GD, coinfection with HIV leads to an aggressive form of renal disease that can be easily confused with HIV-associated nephropathy. Although hypocomplementemia, cryoglobulinemia, and more prominent hypertension and microscopic hematuria may provide clues to the presence of HCV-GD, renal biopsy is essential to differentiate HCV-GD from HIV-associated nephropathy.

Infection with hepatitis C virus (HCV) is the major cause of non-A, non-B hepatitis and may lead to chronic active hepatitis, cirrhosis of the liver, and hepatocellular carcinoma (1,2). Chronic HCV infection is also associated with a variety of extrahepatic manifestations, such as cryoglobulinemia, porphyria cutanea tarda, sicca-like syndrome, and glomerulonephritis (3–12). The glomerular diseases associated with HCV infection (HCV-GD) are usually expressed histopathologically as membranoproliferative glomerulonephritis (MPGN) or membranous glomerulopathy (MGN) (9–12). The clinical features of HCV-GD have been described (9–12), but the outcome and the response to specific treatment are not well defined (13,14). Although HCV infection is highly prevalent among intravenous drug users, a population that is also at high risk for coinfection with HIV (15,16), there are few reports of the HCV-GD in HIV-infected patients (17–20). Moreover, the impact of HIV infection on the clinical course and outcome of HCV-GD is unknown. In this study, we present the clinical features, renal histopathology, and outcome of 14 HIV-infected patients with HCV-GD.

Materials and Methods

Between January 1994 and November 1997, 14 patients with HIV infection who also had HCV-GD were identified retrospectively from the archives of the Nephropathology Laboratory of Columbia University. Seven patients were seen at Harlem Hospital Center, four at Columbia Presbyterian Medical Center, two at St. Luke-Roosevelt Hospital in New York City, and one at Morristown Hospital in New Jersey. The medical records of all patients were reviewed with particular attention to laboratory studies, parameters of HIV infection, treatment, and outcome. In all cases, chronic HCV infection was documented by the presence of serum antibodies against HCV proteins using second generation enzyme immunoassay (ABBOTT HCV EIA 2.0) and/or the recombinant immunoblot assay (RIBA); in three cases, confirmation by PCR for HCV RNA was performed. HIV infection was diagnosed by the presence of serum antibodies against HIV using enzyme-linked immunosorbent assay followed by confirmation with Western blot. All patients underwent percutaneous renal biopsy, and all renal specimens were processed for light microscopy, immunofluorescence, and electron microscopy according to standard techniques. In addition, two patients (patients 1 and 7) had post mortem examinations. Each patient was followed over time for the development of specific end points, including progression to advanced renal failure, initiation of dialysis, and death. The clinical course of these patients and their response to treatment were evaluated by plotting serial serum creatinine concentrations over time. AIDS was

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defined according to the 1993 revised Centers for Disease Control and Prevention classification system (21). Progression to advanced renal failure was defined as a doubling of baseline serum creatinine and/or an increase in serum creatinine to above 4 mg/dl.

A group of 105 Italian patients with essential mixed cryoglobulinemic glomerulonephritis reported by Tarantino *et al.* were chosen as historical controls (22). Within this group, 85% of the 34 patients tested for anti-HCV antibodies were positive. Although this cohort clearly differed from ours with respect to demographic features and prevalence of anti-HCV antibodies, this historical control group provides the most detailed data available regarding long-term renal outcome of HCV infection (22).

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS 7.5 for Windows) was used for statistical analyses. Group data were expressed as mean ± SD for continuous variables with Gaussian distribution or as median and ranges for variables with skewed distribution. For categorical variables, the results were expressed as percentage or ratio. Differences in the group results between this patient cohort and historical controls were evaluated by *t* test or χ^2 analysis. The actuarial survival was calculated by the method of Kaplan and Meier (23), and comparison between survival curves was made by the log-rank test.

Results

Clinical Features

The demographic profile, clinical presentation, laboratory findings, clinical course, and outcome of 14 HIV-infected patients with HCV-GD are summarized in Table 1. These included 8 men and 6 women, with a mean age of 45.2 ± 6.7 yr. Thirteen of 14 patients (93%) were African-Americans. All gave a history of intravenous drug use. None had circulating hepatitis B virus (HBV) surface antigen but all had HBV antibodies. All were seropositive for HIV infection: 12 patients (86%) had known history of HIV infection for an average of 4.8 ± 3.3 yr and the remaining two patients (14%) were diagnosed with HIV infection at the time of renal evaluation. The mean CD4+ T cell counts were 238 ± 167/μl. Six patients (43%) had AIDS at the time of renal presentation.

The reasons for renal referral were nephrotic syndrome or nephrotic proteinuria with renal insufficiency in 10 patients (71%), chronic renal insufficiency in two (14%), acute renal failure in one (7%) and uremia in one (7%). Hypertension, defined as systolic BP (SBP) of 140 mmHg or greater or diastolic BP (DBP) of 90 mmHg or greater was noted in eight patients (57%) and included stage 1 in two patients (SBP 140 to 159 or DBP 90 to 99), stage 2 in three patients (SBP 160 to 179 or DBP 100 to 109), and stage 3 in three patients (SBP ≥ 180 or DBP ≥ 110) (24). Eight patients (57%) had peripheral edema, which was massive in six (43%). No patient had palpable purpura or arthritis.

Urinalysis with microscopic examination of the urine sediment showed 3 to 4+ proteinuria in 12 patients (86%) and microhematuria in 13 patients (93%) with red cell casts in three patients. The mean 24-h urine protein was 8.4 ± 8.2 g, and the mean creatinine clearance at the time of renal biopsy was 34.6 ± 17.1 ml/min.

The mean values of serum chemistries at the time of renal biopsy were: creatinine 3.5 ± 3.9 mg/dl, albumin 2.3 ± 0.8 g/dl, and cholesterol 150 ± 60 mg/dl. The liver enzymes were mildly elevated in 11 patients (79%): The mean serum aspartate aminotransferase was 74 ± 35 U/L (normal <40 U/L), and the mean alanine aminotransferase was 32 ± 19 U/L (normal < 36 U/L). Only one patient (patient 5) had clinically acute liver disease with jaundice. All patients were anemic with the mean hematocrit of 29.2 ± 3.9%. Hypocomplementemia was present in six of 13 patients (46%) and cryoglobulinemia was detected in four of 12 patients (33%). Rheumatoid factor was present in two of 9 patients (22%) tested.

Renal Pathology

The renal biopsy findings are summarized in Table 2. The major pattern of glomerular disease was MPGN, including six cases of MPGN type 1 and five cases of MPGN type 3, of the Burkholder subtype. One patient with MPGN type 3 was further subcategorized as an unusual example of immunotactoid glomerulopathy (described in detail in reference (25)). The remaining three patients had MGN with atypical features.

Among the six patients with MPGN type 1, all displayed varying degrees of mesangial proliferation with peripheral mesangial interposition, duplication of glomerular basement membrane, and accentuated glomerular lobularity (Figure 1). In two of these cases, crescents were identified involving 5 and 17% of glomeruli, respectively. The major immune reactants detected by immunofluorescence were IgM (six patients), IgG (five patients), C3 (six patients), and C1 (four patients), with only sparse and weak staining for IgA (three patients). On ultrastructural evaluation (available in five patients), deposits were typically in combined mesangial and subendothelial locations. In three patients, occasional subepithelial deposits were also seen, but without sufficient number or regularity to qualify as MPGN type 3. No case of MPGN type 1 had organized deposits (with tubular or fibrillar substructure) at the ultrastructural level. One patient (patient 9) lacked any detectable electron-dense deposits by electron microscopy in spite of well-developed membranoproliferative features by light microscopy and 2+ glomerular staining for IgM, C3, and C1. This patient also had had a recent episode of microangiopathic hemolytic anemia with schistocytes identified in the peripheral blood smear, acute thrombocytopenia, and anemia. The combination of clinical and renal biopsy features suggested the possibility of a membranoproliferative pattern secondary to subacute thrombotic microangiopathy, although no actual fibrin thrombi were detected.

MPGN type 3 of the Burkholder subtype, identified in five patients, presented a mixed pattern of membranoproliferative and membranous glomerulonephritis (Figure 2). The membranous component was visible by light microscopy as variably thickened and rigid glomerular basement membranes with spikes or internal vacuolizations, often superimposed on double-contoured basement membranes. Two of the five patients had crescents involving 19 and 41% of glomeruli, respectively. By immunofluorescence, four had codeposits of IgG and IgM and one had IgM as the only Ig deposited. All five patients

Table 1. Clinical features, course, and outcome of HCV-associated glomerular diseases in HIV patients[a]

Characteristic	Patient													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age/gender/race	51/M/B	44/M/B	55/F/B	42/F/B	40/M/B	58/M/B	48/F/B	37/M/H	44/F/B	37/M/B	44/F/B	52/M/B	43/F/B	38/M/B
HBV sAg/sAb/cAb	−/−/+	−/−/+	−/−/+	−/+/	−/−/+	−/−/+	−/+/+	−/+/+	−/−/+	−/−/+	−/−/+	−/+/+	−/−/+	−/+/
CD4+ T cells/μl	503	575	36	38	410	98	324	238	160	74	270	146	250	213
Presentation	NS	NS	RI	NS	ARF	RI	NS	RI	RI	RI	NS	RI	NS	Uremia
BP (mmHg)	150/110	160/100	140/100	110/70	105/55	142/89	165/90	94/52	110/80	100/74	190/110	110/88	150/90	163/114
Edema	3+	3+	No	3+	No	No	3+	1+	No	No	3+	1+	3+	No
Proteinuria (g/24 h)	12.8	17.4	5.6	3.3	3.4	3.8	13.7	0.3	3.2	4.7	24	0.04	23	2.7
Microhematuria	3+	3+/C	2+	3+/C	3+/C	2+	3+	2+	1+	0	1+	1+	3+	2+
Cr (mg/dl) at Bx	2.5	3.0	4.2	1.8	2.0	2.4	2.6	1.6	2.1	3.0	2.4	1.8	2.2	16.7
C_{Cr} (ml/min)	30.3	57.0	19.3	37.0	40.0	19.9	21.2	51.8	21.0	28.6	47.0	68.1	37.2	5.9
S. albumin (g/dl)	1.2	2.2	3.6	2.0	2.3	3.0	1.2	3.2	2.1	2.2	1.0	3.1	3.0	2.6
S. cholesterol (mg/dl)	174	248	149	196	52	141	141	90	110	125	267	135		116
AST/ALT (U/L)	73/35	52/18	50/13	108/36	127/62	89/57	46/17	34/16	120/26	103/44	23/6	74/45	101/60	29/14
Hypocomplementemia	No	No	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	ND	No
Cryoglobulinemia	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No	ND	ND
Renal pathology	MPGN-1	MPGN-3	MGN & FSGS	Exudative & MGN	MPGN-3	MPGN-3	MPGN-1	Mes. Prolif. & Seg. MGN	MPGN-1 (?TMA)	MPGN-1	MPGN-3 (IT)	MPGN-1	MPGN-1	MPGN-3
Peak Cr (mg/dl)	16.5	10.4	9.2	2.3	7.0	11.6	4.7	2.3	4.1	6.8	6.3	1.9	4.6	16.2
t (months) to peak Cr	2.2	2.1	5.8	0.3	−0.4	5.3	0.2	6.7	1.1	0.4	1.7	NA	10.2	0.0
Dialysis	PD	HD	HD	No	No	HD	No	No	No	?	HD	No	No	HD
t (months) to dialysis	2.4	2.1	5.8	NA	NA	22.4	NA	NA	NA	NA	1.8	NA	NA	0.0
Outcomes	Death	Death	Death	Death	Alive	Death	Death	Alive	Death	Lost	Alive	Death	Alive	Alive
t (months) of follow-up	9.3	45.9	6.1	0.6	28.5	25.4	0.2	28.6	6.0	0.4	20.5	6.4	10.4	5.9

[a] M, male; F, female; B, black; H, Hispanic; HBV, hepatitis B virus; sAg, surface antigen; sAb, surface antibody; cAb core antibody; NS, nephrotic syndrome; RI, renal insufficiency; ARF, acute renal failure; C, red cell casts; Cr, serum creatinine; AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; Bx, biopsy; C_{Cr}, creatinine clearance; S, serum; ND, not done; MPGN-1, type 1 membranoproliferative glomerulonephritis; MPGN-3, type 3 membranoproliferative glomerulonephritis; MGN, membranous glomerulopathy; FSGS, focal segmental glomerulosclerosis; Mes. Prolif., mesangial proliferative; Seg., segmental; TMA, thrombotic microangiopathy; IT, immunotactoid glomerulopathy; NA, not applicable; *t* (months), time interval in months; PD, peritoneal dialysis; HD, hemodialysis.

Table 2. Renal biopsy findings[a]

Analysis	Patient													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Light microscopy														
no. of glomeruli	36	21	12	31	18	18	7	23	18	12	5	42	17	17
no. of sclerotic glomeruli	3	9	8	1	1	5	0	6	2	5	0	2	4	14
no. of crescents	2 (1 cell; 1 fibr)	4 (1 cell; 3 fibr)	None	None	None	None	None	None	None	None	None	None	3 (2 cell; 1 fibr)	7 (3 cell; 4 fibr)
Tubular atrophy/ interstitial fibrosis	Mod	Severe	Severe	None	None	Mod	Mod	Severe	Mild	Mod	Mild-mod	Mild	Mild	Severe
Immunofluorescence														
IgG	3+Mes/ CW	3+CW	1+Mes/ CW	2+CW	Neg	1+Mes/ CW	2+Mes/ CW	Neg	Neg	1+Mes	3+Mes/CW	2+Mes/ CW	1+Mes/ CW	1+CW
IgM	1+Mes/ CW	1+Mes/ CW	Neg	2+Mes/ CW	1+Mes/ CW	1+CW	2+Mes/ CW	Neg	2+Mes	3+Mes/ CW	2+CW	2+Mes/ CW	2+Mes/ CW	2+CW
IgA	+/−Mes/ CW	Neg	Neg	+/−CW	Neg	Neg	Neg	Neg	Neg	1+Mes	1+CW	Neg	1+CW	Neg
C3	3+Mes/ CW	2+CW	Neg	1+Mes/ CW	3+Mes/ CW	1+CW	3+Mes/ CW	1+Mes/ CW	2+Mes/ CW	3+Mes/ CW	+/−CW	3+Mes/ CW	3+Mes/ CW	2+CW
C1	1+CW	1+CW	Neg	3+Mes/ CW	Neg	Neg	1+CW	Neg	2+Mes/ CW	Neg	Neg	Neg	+/−CW	1+CW
Electron microscopy														
location of deposits														
mesangial	2+	2+	1+	2+	1+	3+	NA	2+	Neg	2+	3+(fibrils)	2+	2+	1+
subendothelial	2+	+/−	Neg	Neg	1+	1+		1+	Neg	2+	3+(fibrils)	1+	2+	2+
subepithelial	+/−	3+	2+	3+	1+	3+		1+	Neg	Neg	3+(fibrils)	1+	1+	2+
TRI	2+	None	1+	None	None	3+		None	3+	None	1+	1+	3+	2+
Final diagnosis	MPGN type 1	MPGN type 3	MGN & FSGS	Exudative & MGN	MPGN type 3	MPGN type 3	MPGN type 1	MesP & sMGN	MPGN type 1 (? TMA)	MPGN type 1	MPGN type 3 (IT)	MPGN type 1	MPGN type 1	MPGN type 3

[a] Immunofluorescence and electron microscopy are graded on a scale of 0 to 3+. cell, cellular crescent; fibr, fibrous crescent; Mod, moderate; Mes, mesangial; CW, glomerular capillary wall; Neg, negative; NA, not available; TRI, tubuloreticular inclusions; MPGN, membranoproliferative glomerulonephritis; MGN, membranous glomerulopathy; FSGS, focal segmental glomerulosclerosis; MesP & sMGN, mesangial proliferative with segmental membranous features; TMA, thrombotic microangiopathy; IT, immunotactoid.

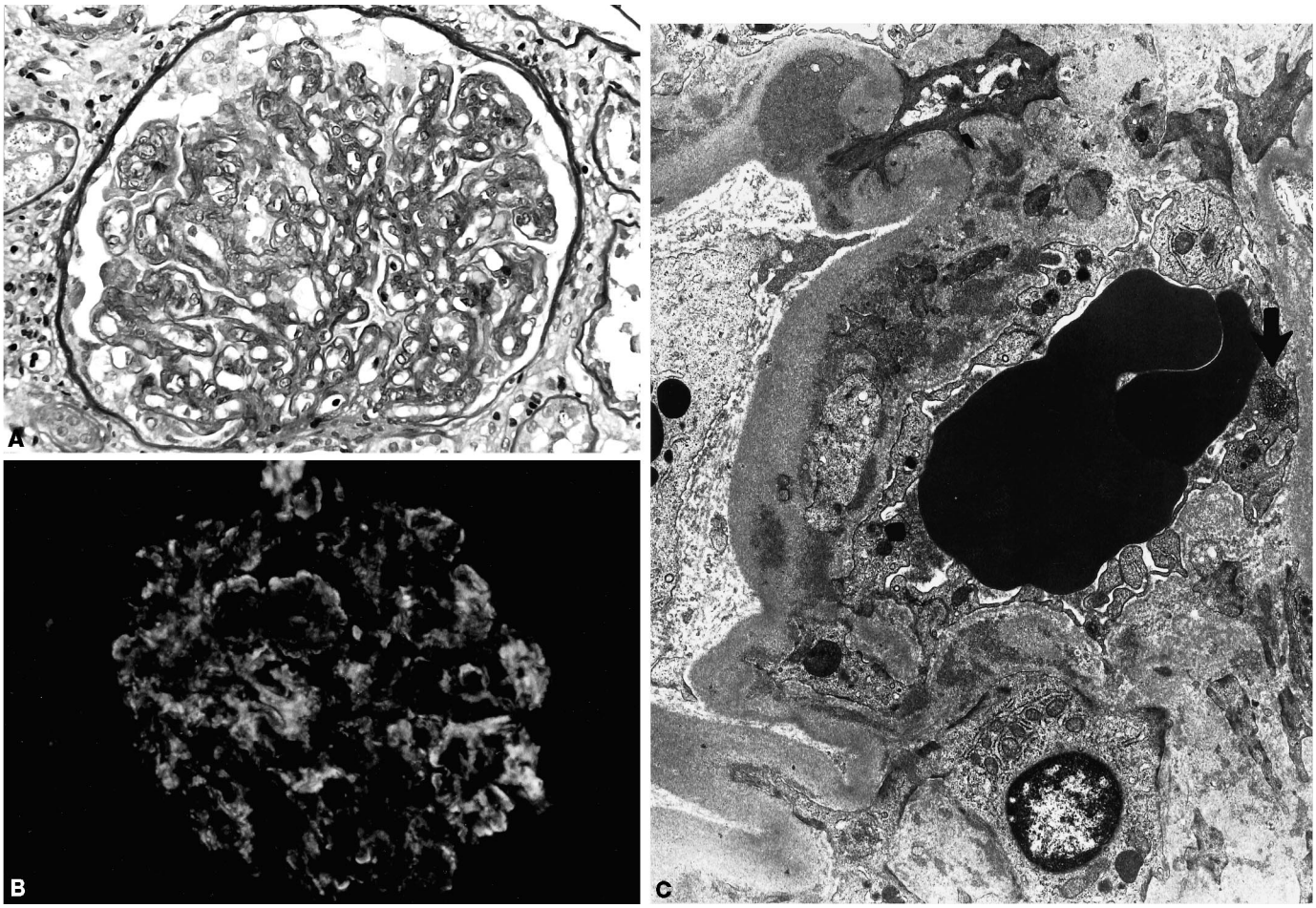

Figure 1. Membranoproliferative glomerulonephritis type 1. (A) A glomerulus from patient 1 shows global mesangial hypercellularity with peripheral mesangial interposition and segmental duplication of glomerular basement membranes. Periodic acid-Schiff stain, ×260. (B) Immunofluorescence from the same case (patient 1) showing global mesangial and subendothelial positivity for C1 in a lobular pattern. Fluorescence micrograph, ×260. (C) An electron micrograph from patient 13 showing narrowing of the glomerular capillary lumen by circumferential mesangial interposition, producing a double contour. Electron-dense deposits are present in the expanded mesangial matrix and in the subendothelial region. A single subepithelial deposit is also seen. The glomerular endothelium contains a tubuloreticular inclusion (arrow). Electron micrograph, ×5000.

demonstrated deposits of C3, and three also had positivity for C1. By electron microscopy, deposits were in combined mesangial, subendothelial, and subepithelial locations. The only specimen with organized deposit substructure was from patient 11 with immunotactoid glomerulopathy (25). In this patient, electron microscopy disclosed voluminous deposits of stacked tubular structures ranging from 35 to 45 nm in diameter in the subendothelial, subepithelial, and mesangial locations.

Among the three patients with MGN, all displayed morphologic features atypical for idiopathic MGN. In one patient, there was focal segmental and global glomerulosclerosis with collapsing features and podocyte reactivity suggesting overlap with HIV-associated nephropathy (HIVAN). One patient had a segmental MGN with diffuse mesangial proliferative features and abundant mesangial deposits detected by electron microscopy. The third patient had MGN with focal segmental endocapillary proliferative and exudative glomerulonephritis characterized by many infiltrating neutrophils, but without mesangial interposition or duplication of the glomerular basement membranes. In all three patients, deposits were detected in the subepithelial and mesangial regions. A few subendothelial deposits were also identified in the patient with mesangial proliferative features. No patient had organized deposits. By immunofluorescence, deposits consisted of IgG alone in one patient, C3 alone in one patient, and combined deposits of IgG, IgM, IgA, C3, and C1 in the patient with membranous and exudative glomerulonephritis.

Post mortem examination in two patients (patients 1 and 7) showed micronodular cirrhosis of the liver and persistent MPGN with similar histologic features to those noted in the previous renal biopsies.

Clinical Course and Outcome

Follow-up was available in 13 patients (93%) and ranged from 1 wk to 46 mo (mean 14 mo) after renal biopsy. Table 1 summarizes the time intervals from the diagnosis of HCV-GD to the development of the specific end points of advanced renal failure, initiation of dialysis, and death.

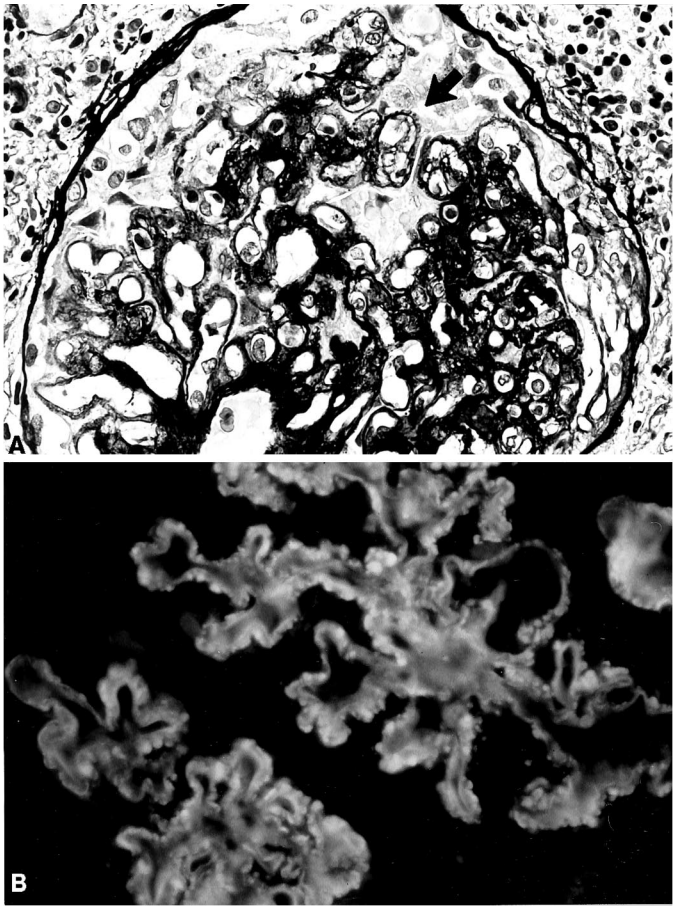

Figure 2. Membranoproliferative glomerulonephritis type 3. (A) A glomerulus from patient 2 shows mixed proliferative and membranous features with an overlying cellular crescent. There are focal double contours of the glomerular basement membrane as well as numerous subepithelial spikes (arrow). Jones methenamine silver stain, ×400. (B) Immunofluorescence from the same case (patient 2) showing prominent granular subepithelial deposits of IgG as well as mesangial and subendothelial deposits. Fluorescence micrograph, ×480.

Advanced renal failure, defined by a doubling of baseline serum creatinine concentration and/or an increase in serum creatinine above 4 mg/dl, developed in 10 patients (71%). One of these patients (patient 14) was already on dialysis when a renal biopsy was obtained. Five patients (43%) progressed to dialysis within a median time of 2.4 mo (range, 1.8 to 22.4 mo). Among the six patients on dialysis, four died within a median time period of 5.0 mo on dialysis (range, 0.3 to 43.8 mo). The causes of death were uremia in one (patient 1 who refused further dialytic therapy), sepsis in two (patients 2 and 3), and metastatic adenocarcinoma of the lung in one (patient 6). The remaining two patients were on dialysis for 5.9 and 20.5 mo, respectively. Among the remaining four patients with advanced renal failure not requiring dialysis, two died of nonrenal causes (patient 7 of pneumonia and drug intoxication; patient 9 of end-stage AIDS), one showed continued worsening of renal function, and one with AIDS was lost to follow-up.

For the four patients with relatively stable renal function, two died within a period of 0.6 and 6.4 mo, respectively, after biopsy. The causes of death were pulmonary hypertension with right heart failure in one (patient 4) and unknown in the other (patient 12). The remaining two patients (patients 5 and 8) are alive with stable renal function at 28.5 mo and 28.6 mo, respectively, after renal biopsy.

A Kaplan–Meier survival curve for all 14 patients using dialysis or death as the end point is shown in Figure 3. Survival analysis of the historical controls (22) was superimposed on that of the present cohort for visual comparison. The median time to dialysis or death among the HIV-infected patients with HCV-GD was 5.8 mo (95% confidence interval, 1.3 to 10.3 mo). In comparison, Tarantino *et al.* reported a 49% 10-yr survival (free of death or chronic renal failure) in 105 patients with essential mixed cryoglobulinemic glomerulonephritis (22). Further stratification of the present cohort into AIDS *versus* non-AIDS groups revealed a higher mortality and a significantly shorter survival time for AIDS patients regardless of whether they received dialysis. Five of six AIDS patients (83%) were dead at the close of the study *versus* three of eight non-AIDS patients (38%). The median patient survival time was 6.1 mo for the AIDS group *versus* 45.9 mo for the non-AIDS group (log-rank test $P = 0.02$).

α-Interferon was administered to three patients. The regimen consisted of 3 million units given subcutaneously 3 times per week for 6 mo. One patient (patient 2) completed a full course of treatment. In one patient (patient 3), treatment was discontinued after 5 mo because of the development of advanced renal failure. In the third patient (patient 6), the treatment was discontinued after 3 mo because of severe mental depression. No improvement in renal function or survival time was noted in any of the three patients. Angiotensin-converting enzyme (ACE) inhibitor was not used (except for patient 12) because of the high prevalence of moderately advanced renal insufficiency and/or hyperkalemia. Glucocorticoids were only used for adjunct therapy of pneumocystis carinii pneumonia with hypoxemia.

In summary, at the close of this study, eight patients (57%)

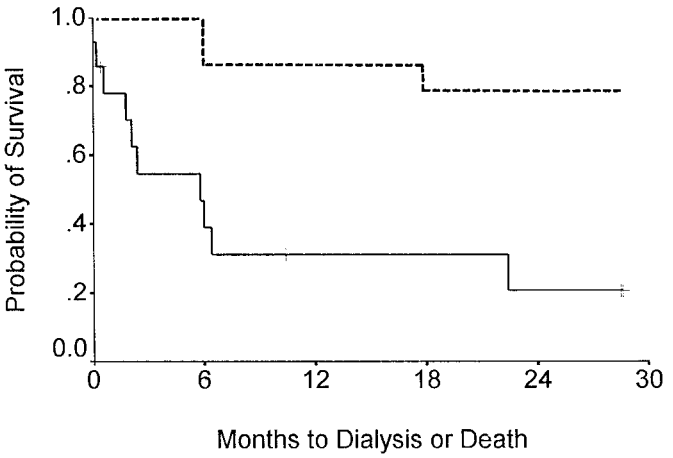

Figure 3. Survival curve of HIV-infected patients with HCV-associated glomerular disease (—) compared with that of historical controls with essential mixed cryoglobulinemic glomerulonephritis (- - -) (22). + indicates censored patient.

were dead with median survival of 6.1 mo, five patients (36%) were alive, and one patient (7%) was lost to follow-up.

Discussion

Despite the high prevalence of both HCV and HIV infection among intravenous drug users (15,16), there are few reports of HCV-GD in HIV-infected patients (17–20). The rarity of this entity may relate to HIV-induced immunosuppression with reduced ability to mount a sufficient immune response to HCV to develop immune complex-mediated glomerular disease. Alternatively, the development of HIVAN may have led to end-stage renal failure before the development of the requisite immune response for HCV-GD. Indeed, glomerulonephritis is a relatively late complication of HCV infection. Likewise, death due to AIDS may supervene before HCV-GD becomes manifest. Finally, HCV-GD in HIV-infected patients may be underdiagnosed because of the assumption that the renal disease is attributable to HIVAN and the resultant underutilization of renal biopsy in this population.

Stokes *et al.* reported 12 HIV and HCV coinfected intravenous drug users, seven blacks and five Hispanics, who presented with proteinuria, microhematuria, and elevated serum creatinine (20). Edema, hypertension, and hypocomplementemia were noted in the majority of patients, and 42% of patients had cryoglobulinemia (20). Renal biopsy showed MPGN in five, mesangial proliferative glomerulonephritis in five, MGN in one, and collapsing glomerulopathy with immune complex deposits in one patient (20). Three patients died and five patients progressed to end-stage renal failure in the course of follow-up with a mean time to dialysis of 8.4 mo after biopsy (20). Our cohort differs from that of Stokes *et al.* with respect to the greater percentage of African-Americans (93%) and the lower prevalence of hypocomplementemia (46%) and cryoglobulinemia (33%) despite a higher prevalence of MPGN. Overall, morbidity and mortality were higher in our patients, with median combined renal/patient survival of only 5.8 mo. The majority of our patients died with renal failure, but the major causes of death were nonrenal and related to complications of long-term HIV infection. Although we observed a similar spectrum of glomerular lesions, our patients had a particularly high prevalence of MPGN type 3, a more complex glomerular lesion characterized by mesangial, subendothelial, and subepithelial deposits. Although cryoglobulinemia was detected in 33% of patients in this study, only one patient had organized deposits. These findings differ from the high rate of substructure identification in glomerular deposits of HCV-GD from non-HIV-infected patients (9,13).

In our patients with HCV and HIV coinfection, the HCV-GD became clinically evident in the setting of moderately to far-advanced HIV infection. Eighty-six percent of the patients had CD4+ T cells below 500/μl and 43% of patients had AIDS. The majority of patients presented with nephrotic syndrome or nephrotic proteinuria and renal insufficiency. These clinical presentations are similar to those reported for patients with HCV-associated MPGN (HCV-MPGN) without HIV coinfection (9,13). However, the degree of renal insufficiency in these HIV-infected patients with HCV-GD was more advanced than reported in patients with HCV-MPGN (9,13). The mean serum creatinine was significantly higher (3.5 mg/dl *versus* 1.8 mg/dl, $P < 0.025$), and the mean creatinine clearance was significantly lower (35 ml/min *versus* 51 ml/min, $P < 0.05$) in our HIV-infected patients with HCV-GD compared to reported patients with HCV-MPGN without HIV (9,13). Despite massive proteinuria with severe hypoalbuminemia and edema, hypercholesterolemia was typically absent, as described for HIVAN (26). Hypocomplementemia and/or cryoglobulinemia were present in less than half of the patients, a lower prevalence than reported in HCV-GD without HIV coinfection (9,13). Thus, the absence of hypocomplementemia, cryoglobulinemia, or rheumatoid factor cannot reliably exclude HCV-GD in HIV-infected patients.

Studies of the clinical course of cryoglobulinemic glomerulonephritis, a form of MPGN induced by HCV, have described a predominantly chronic and indolent course with variable episodes of acute exacerbations and remissions (22,27,28). Progression to end-stage renal failure requiring dialysis was unusual, and chronic uremia developed in only 10% of the patients several years after the onset of renal symptoms (27,28). The cumulative 10-yr survival without renal failure was 49% (22). Among the subgroup with initial serum creatinine >1.5 mg/dl, the 30-mo renal survival was 60% (22). A study on the effect of α-interferon therapy in patients with HCV-GD showed a significant reduction in proteinuria and an improvement in serum creatinine of 0.2 mg/dl or greater in 11 of 14 patients over 6 to 12 mo (13). By contrast, 71% of our HIV-infected patients with HCV-GD progressed rapidly to advanced renal failure, and 50% of them required dialysis within a median interval of 2.3 mo after biopsy. Although all of our patients had creatinine values greater than 1.5 mg/dl at diagnosis, outcome was far worse than for the subgroup of historical controls with similar initial creatinine levels (21% *versus* 60% 30-mo survival). Mortality was high (57%) with median renal/patient survival of only 5.8 mo. α-Interferon treatment in three patients did not prevent the development of renal failure, nor did it prolong patient survival. This pattern of rapid deterioration of renal function mimics the clinical course of HIVAN (26,29,30). Although the presence of hypertension, microscopic hematuria with active urine sediment, and hypocomplementemia may serve as clues to the possible presence of glomerulonephritis, the distinction between HCV-GD and HIVAN can only be made by renal biopsy.

The causes of this poor outcome and the resistance to α-interferon treatment remain speculative. Only one patient had overlapping features of collapsing glomerulopathy and HCV-GD. Although crescents were identified in four cases, these involved a minority of glomeruli. The large percentage of glomeruli with complex glomerular lesions, particularly MPGN type 3, may have influenced the poor renal survival. Sepsis as the leading cause of death suggests that double viral load and a possible increase in HIV viral RNA in advanced renal failure (31) contributed to higher mortality. Progressive glomerulosclerosis also may have been promoted by both HIV coinfection and risk factors related to black race. Racial factors, whether biologic or socioeconomic, have been shown to

adversely affect the outcome of other glomerular diseases such as lupus nephritis, HIVAN, and idiopathic collapsing focal glomerulosclerosis (29,32–35), and may explain some of the observed differences in renal/patient survival in HCV-GD compared to historical controls. In summary, it is likely that the combined influences of complex glomerular lesions, higher baseline renal insufficiency, double viral burden, and black race promote rapid renal deterioration and high mortality in HIV-infected patients with HCV-GD.

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