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Renal Involvement in the Acquired Immunodeficiency Syndrome: Presentation, Clinical Course, and Therapy

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Acute renal failure developing during the clinical course of the acquired immunodeficiency syndrome (AIDS) has been related to complications of sepsis, nephrotoxic antibiotics, and recently to the development of glomerular lesions. Of 114 AIDS patients admitted to our hospital between January 1985 and June 1986, 11 patients (9.6%) developed acute renal failure. None of these 11 patients had a history of intravenous drug abuse or hypertension. All patients were male with an average age of 35 years old, 81% were black, and all were bisexual or homosexual. Renal failure was attributed to AIDS-related focal glomerulosclerosis (five cases), prerenal azotemia (one case), acute interstitial nephritis (one case), and acute tubular necrosis (four cases). Approximately 15 weeks elapsed from the onset of renal failure to end-stage kidney disease. Only one of five patients survived more than six months after beginning dialysis. Acute renal failure is an important complication of AIDS with glomerular involvement detected in 45% of patients. The long-range problems of initiating and maintaining dialysis therapy in these patients need to be addressed. (Henry Ford Hosp Med J 1987;35:38-41)

The acquired immunodeficiency syndrome (AIDS) is characterized by a state of disordered immunoregulation resulting in the development of opportunistic infections and/or Kaposi's sarcoma. Acute renal failure arising during the course of illness usually has been attributed to complications of sepsis and/or nephrotoxic antibiotics. Until recently, glomerular renal disease was not considered a manifestation of this syndrome. Several centers have reported an increased frequency of the renal lesion of focal segmental glomerulosclerosis (FSGS) in AIDS patients who developed acute renal failure (1-4). Clinically, these patients have massive proteinuria and a rapid progression to end-stage renal failure.

We have analyzed all patients admitted to Henry Ford Hospital with the diagnosis of AIDS in whom acute renal failure was documented. A review of 114 AIDS cases revealed that 11 patients had developed acute renal failure. Renal failure was attributed to AIDS-related glomerulopathy characterized by FSGS (five patients), prerenal azotemia (one patient), acute interstitial nephritis (one patient), and acute tubular necrosis (four patients).

Materials and Methods

We performed a retrospective study of the medical records of 114 patients with a diagnosis of AIDS and renal failure who were evaluated at Henry Ford Hospital from January 1985 to June 1986. Eleven patients with renal failure (defined by a serum creatinine greater than 2.0 mg/dL) were identified. None of these 11 patients were intravenous drug abusers or had a history of hypertension. All were either bisexual or homosexual men.

The diagnosis of AIDS was based on criteria from the Centers for Disease Control (CDC), which consisted of 1) immunologic studies showing positive serology for the HTLV-III virus antibody, and 2) evidence of an opportunistic infection or Kaposi's sarcoma (5,6). Renal tissue was available in six cases: three by percutaneous renal biopsy and three at autopsy. Renal histology material was prepared using hematoxylin-eosin, periodic acid-Schiff, and Jones' stains. Standard immunofluorescence stains and electron microscopic evaluation were performed on selected specimens.

Case Reports

Based on clinical course and laboratory data, one patient had a diagnosis of prerenal azotemia, one had acute interstitial nephritis, four had renal failure secondary to acute tubular necrosis, and five had renal failure due to FSGS (AIDS-related glomerulopathy). Four of the five patients with FSGS had nephrotic range proteinuria; the other patient had 4+ proteinuria on qualitative urinalysis, but a 24-hour urine for protein was not performed. The time from presentation of AIDS-related FSGS to end-stage kidney failure requiring dialysis averaged 15 weeks (range eight to 24 weeks).

Table 1 summarizes the clinical data and causes of renal failure encountered in our 11 patients. The following eight cases were selected for more detailed presentation.

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Table 1
Clinical Characteristics of Study Population

Patient	Age	Sex	Race	Proteinuria	Time to End-Stage Renal Disease (weeks)*	Pathology	Clinical Diagnosis	Current Status
1	22	M	B	4+	16	FSGS	AIDS glomerulopathy	L
2	29	M	B	10.0 g/24°	24	ND	AIDS glomerulopathy	D
3	46	M	W	ND	2	ATN ^A	ATN	D
4	30	M	B	negative	—	ATN ^A	ATN	L
5	35	M	W	1+	—	ND	Interstitial nephritis	L
6	40	M	B	negative	—	ND	Prerenal azotemia	L
7	55	M	B	9.3 g/24°	8	FSGS	AIDS glomerulopathy	D
8	32	M	B	3+	16	FSGS	AIDS glomerulopathy	D
9	22	M	B	1.7 g/24°	—	ND	ATN	L
10	34	M	B	7.3 g/24°	—	FSGS ^A	AIDS glomerulopathy	D
11	28	M	B	negative	4	ND	ATN	D

*Denotes time from the initial elevated serum creatinine to end-stage renal failure requiring dialysis.
FSGS = focal segmental glomerulosclerosis, ATN = acute tubular necrosis, L = living, D = dead, ND = not done, and ^A = autopsy.

Case 1

A 22-year-old black man was diagnosed as having AIDS in 1985 when he developed *Pneumocystis carinii* pneumonia (PCP). A renal biopsy, performed when he developed 4+ proteinuria on qualitative urinalysis, revealed FSGS (Figure). His renal function deteriorated rapidly, and he required hemodialysis four months after presentation. The patient was switched to chronic ambulatory peritoneal dialysis (CAPD) in April 1986 and is currently doing well. AIDS-related FSGS was considered responsible for his renal failure.

Case 2

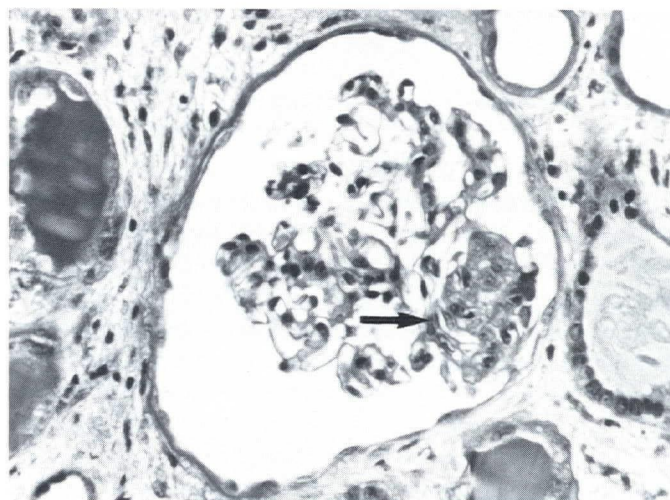
A 29-year-old black man was diagnosed as having AIDS in 1984 when he developed PCP. His BUN and creatinine at that time were 10 mg/dL and 0.9 mg/dL, respectively. He was hospitalized in December 1985 for cytomegalovirus (CMV) pneumonia and was found to have a BUN of 41 mg/dL and a creatinine of 5.0 mg/dL. No potentially nephrotoxic medication was given prior to this hospitalization. A 24-hour urine collection revealed proteinuria of 10 g. His renal function deteriorated rapidly, and hemodialysis was initiated in May 1986 when the BUN was 70 mg/dL and the serum creatinine was 14.3 mg/dL. The patient died soon afterward from complications related to sepsis. Permission for an autopsy was denied. Although renal tissue for histologic examination was not available, the history of rapid deterioration in renal function associated with massive proteinuria and normotension made AIDS-related FSGS likely.

Case 4

A 30-year-old black man was admitted with PCP, disseminated cryptococcal infection, and Kaposi's sarcoma. Amphotericin B and trimethoprim-sulfamethoxazole (TMP-SMX) were started. The initial BUN of 9 mg/dL and creatinine of 0.8 mg/dL rose to 30 mg/dL and 2.7 mg/dL, respectively, after ten days. The patient was clinically euvolemic with good urine output. No eosinophiluria, eosinophilia, or proteinuria was noted. The dosage of amphotericin B was decreased, and the serum creatinine gradually returned to baseline levels. Non-oliguric acute tubular necrosis secondary to amphotericin B was the most likely diagnosis.

Case 5

A 35-year-old white man was hospitalized for treatment of PCP. His creatinine level at admission was 1.0 mg/dL. Shortly after starting treat-



Figure—Glomerulus demonstrating segmental sclerosis (arrow) (periodic acid-Schiff stain) (X100).

ment for his pneumonia with TMP-SMX, the serum creatinine began to rise and peaked at 5.0 mg/dL. The differential WBC count showed 27% eosinophils, and a qualitative urinalysis showed 1+ protein (100 mg/dL). After TMP-SMX was discontinued, the patient's eosinophilia cleared and renal function returned to baseline (1.2 mg/dL) in four weeks. A presumptive diagnosis of acute interstitial nephritis was made.

Case 6

A 40-year-old black man admitted with intractable nausea, vomiting, and diarrhea was found to have a BUN and creatinine of 96 mg/dL and 4.3 mg/dL, respectively. Urinary sediment was unremarkable, and the fractional excretion of sodium was less than 1%. Rehydration with normal saline resulted in a return of creatinine to 1.2 mg/dL at discharge. Prerenal azotemia was considered responsible for his initial abnormal serum chemistry.

Case 7

A 55-year-old black man was diagnosed as having AIDS after he developed PCP. A renal biopsy, performed to determine the cause of massive proteinuria (9.3 g/24^o), showed a histologic diagnosis of FSGS. His renal function deteriorated rapidly over eight weeks, and he died after refusing dialysis therapy.

Case 8

A 32-year-old black man who had AIDS diagnosed following PCP developed 3+ proteinuria on routine urinalysis. A renal biopsy showed FSGS. End-stage renal failure requiring dialysis subsequently developed over a 16-week period. He was switched to CAPD but developed *Candida* peritonitis, requiring a return to hemodialysis therapy. His condition deteriorated rapidly, and he died shortly thereafter.

Case 11

A 28-year-old black man was admitted in a moribund state with a creatinine of 0.9 mg/dL. Disseminated *Mycobacterium avium-intracellulare* was diagnosed after several blood cultures were found to be positive. Treatment was initiated with multiple antibiotics including clofazimine, ethionamide, pentamidine, and amikacin. Despite this treatment, the patient's blood pressure remained low and increasing doses of vasopressors for support were required. Serum BUN and creatinine rose to 124 mg/dL and 4.9 mg/dL, respectively. Acute tubular necrosis due to hypotension and sepsis was diagnosed, and the patient died before dialysis was initiated.

Discussion

In 1984, Rao et al reported that 11 of 92 patients with AIDS developed acute renal failure (1). When factors known to contribute to renal failure were eliminated, such as hypertension, intravenous drug abuse, nephrotoxic medications, and interstitial nephritis, four of the 11 patients had no obvious cause for renal failure. Renal biopsy showed that these patients had FSGS with segmental deposition of IgM and C₃. These lesions were identical to those seen in heroin nephropathy, reflux nephropathy, and idiopathic focal and segmental glomerulosclerosis (7). Data showed that the mean time from presentation to uremia (requiring dialysis) was much shorter in AIDS-related FSGS (3.5 months) compared to FSGS from all other etiologies (43 months). When considering our cases of acute renal failure in AIDS patients, it becomes apparent that a variety of etiologic factors are responsible (Table 2).

Prerenal azotemia occurs in many patients with AIDS who develop intractable diarrhea and/or vomiting. Because of their overall poor state of health, they are unable to adequately replenish fluid losses and soon a state of volume contraction

ensues, resulting in decreased renal perfusion. An accurate assessment of fluid status by history and physical examination will reveal dehydration as a cause of the rising BUN and creatinine. Generous fluid replacement will restore renal function to baseline in the majority of these patients. A normal urinalysis with high specific gravity and low urinary sodium should suggest this diagnosis.

Allergic interstitial nephritis, characterized by acute renal insufficiency, is commonly due to drug exposure (ie, penicillins, sulfa drugs, cephalosporins, and rifampin). Patients with AIDS are routinely exposed to a variety of these antimicrobial agents required for treatment of their opportunistic infections. The spectrum of clinical findings which includes maculopapular rash, persistent low-grade fever, and eosinophilia and/or eosinophiluria with minimal proteinuria (< 1.5 g/24^o) should raise suspicion of this diagnosis. Discontinuation of the responsible medication usually will result in improvement of renal function.

Renal failure from acute tubular necrosis (ATN) can result from either hemodynamic or nephrotoxic injury in AIDS patients. The more common nephrotoxins include diagnostic (x-ray contrast material) and therapeutic interventions (aminoglycosides, amphotericin B, and pentamidine). Hemodynamically mediated ATN may result from prolonged renal hypoperfusion due to dehydration or from peripheral vasodilation and hypotension from sepsis. All these factors lead to a rapid decline in renal function and require prompt removal of the causative agents and supportive care (including dialysis) until tubular recovery occurs and adequate renal function is reestablished.

The diagnosis of AIDS-related FSGS should be considered after all other, more common causes of reversible renal failure have been eliminated. Every effort should be made to investigate and eliminate these causes in patients who are exposed to multiple, potentially nephrotoxic agents and frequent bouts of sepsis.

Patients with AIDS-related FSGS are usually found to be normotensive compared to other patients with FSGS, who tend to be hypertensive (3). None of the five patients with AIDS-related FSGS in our study developed hypertension during their clinical course. Moreover, support of a diagnosis of AIDS-related glomerulopathy can be obtained using renal ultrasound imaging. Schaffer et al showed that patients with AIDS-related FSGS have normal or enlarged kidneys with grade II or III echogenicity (8). Three of our five patients with FSGS had renal ultrasounds. The kidneys were markedly enlarged in one patient, normal-sized in another patient, and decreased in size in the third patient. All had increased echogenicity noted.

Several centers have confirmed that FSGS is the most frequent glomerular finding described in AIDS patients (3,4). Other glomerular lesions include focal and diffuse mesangial proliferation. These lesions are usually associated with a milder degree of proteinuria and less severe renal failure. Patchy interstitial infiltrates secondary to CMV and cryptococcal infection also have been described (1,7,9).

The etiology of the glomerular lesions present in these patients appears to be multifactorial. Electron microscopy and the immunofluorescent studies have demonstrated mesangial

Table 2
Differential Diagnosis of Acute Renal Failure in AIDS Patients

Prerenal azotemia
Allergic interstitial nephritis
Acute tubular necrosis
Circulatory failure and hypotension
Nephrotoxins
AIDS-related glomerulopathy
Focal and segmental glomerulosclerosis
Focal mesangial proliferation
Diffuse mesangial proliferation

deposits both in patients with glomerulopathy and in AIDS patients with histologically normal kidneys (1). The presence of high levels of circulating immune complexes in the sera of AIDS patients and their subsequent renal deposition may play a pathogenic role. Alternatively, nonspecific mesangial trapping of circulating free antigens with in situ immune complex formation may occur. Although no specific circulating antigens have been identified, antigens related to Kaposi's sarcoma have been implicated as a result of the frequent coexistence of this malignancy and renal disease. The precise relationship of these mesangial deposits with the development of FSGS has not been established. No distinct histologic finding has been described in AIDS-related FSGS that would in and of itself establish the diagnosis. This lesion is indistinguishable from that of idiopathic FSGS. Virus-sized structures found in the biopsies of AIDS patients have been reported, but these structures also have been described in FSGS of other etiologies and have not yet been linked to the HTLV-III viron (10).

In the series of patients with AIDS-related nephropathy reported by Rao et al (1) from New York, all affected patients were black, as were the majority of patients (eight of 11) reported in our study. These findings reflect the demographics of the areas studied. Reports from Florida by Gardenswartz et al (2) and Pardo et al (7) show equal numbers of white, black, and Haitian patients with renal disease. Moreover, no correlation has been noted between the presence of AIDS-related glomerular disease and age, sex, homosexuality, intravenous drug abuse, or duration of disease.

Renal disease has a profound effect on the prognosis of these patients. Mortality was found to be 85% over 22 months in patients with renal failure compared to 26% over the same time period in patients with no renal disease (11). In our study, only one of five patients with AIDS-related FSGS survived more than six months after the development of end-stage renal failure. Of the remaining six patients with acute renal failure from other causes, four are still alive at one-year follow-up.

As a result of the dramatic increase in the incidence of AIDS and improvement in diagnosis and treatment of the infections and complications associated with this syndrome, short-term survival of these patients has increased. This may eventually lead to a greater number of patients developing renal failure and requiring chronic dialysis.

Current recommendations from the CDC indicate that either hemodialysis or CAPD are viable options for AIDS patients. Since the HTLV-III virus is highly susceptible to the routine disinfectants used to sterilize dialysis equipment, transmission to noninfected patients within the dialysis unit is unlikely to occur.

In CAPD patients, the large volumes of peritoneal dialysate which result from their daily exchanges have been shown to contain a low level of the HTLV-III virus. However, the infectivity of this solution is considered low, and only standard infection precautions are recommended (12).

The choice of whether to initiate dialysis therapy, either CAPD or chronic hemodialysis, when chronic renal failure supervenes will depend on the patient's state of health and family support. Consultation with the patient and family with a realistic appraisal of their quality of life and prognosis must be considered. Consequently, the problems of initiating and maintaining dialysis therapy in these patients become an important issue.

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