Presentation, pathology, and outcome of HIV associated renal disease in a specialist centre for HIV/AIDS

D I Williams, D J Williams, I G Williams, R J Unwin, M H Griffiths, R F Miller

Objectives: To describe the presentation, pathology, and outcome of biopsy proved renal disease in HIV infected patients at a central London HIV unit from 1992 to 1996.

Methods: Retrospective review of a computerised database and case notes to identify patients with renal disease confirmed by antemortem percutaneous renal biopsy or necropsy.

Results: 17 patients were identified, 13 had biopsy and four necropsy confirmed renal disease. Abnormalities included HIV associated nephropathy (HIVAN) in seven (41%) patients, membranous glomerulonephritis (GN) in four (23%), haemolytic uraemic syndrome (HUS) in two (12%), and interstitial nephritis. The commonest presentation was acute renal failure (ARF) in 10 (59%) patients, chronic renal failure (CRF) in five (29%), and proteinuria alone in two (12%). Although the majority of patients died during the study period (9/13) only three deaths were attributable to their renal disease. Survival ranged in those with HIVAN from 9 to 31 (median 10) months and, in those with membranous GN, from 1 to 46 (median 29) months.

Conclusions: HIVAN was the commonest renal disease found in this group of patients; however, a variety of other pathologies were seen with variable outcomes. All cases of HIVAN were in patients of African or Afro-Caribbean origin and for the majority this was their first presentation of HIV disease. Nephrologists need to be aware of the possibility of HIV infection in patients presenting with renal disease.

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Keywords: HIV infection; AIDS; renal disease; HIV associated nephropathy

Introduction

Renal problems are frequently encountered in the management of patients infected with the human immunodeficiency virus (HIV). Acute renal failure secondary to sepsis, hypotension, or nephrotoxic drugs such as foscarnet or amphotericin B is common and is often potentially avoidable; treatment through the period of renal failure may lead to resolution. Primary renal disease is also associated with HIV infection. In 1984 a specific form of HIV associated primary renal disease was first described. This is known as HIV associated nephropathy (HIVAN) and is characterised clinically by proteinuria, often of sudden onset, with rapidly progressive renal dysfunction resulting in end stage renal disease (ESRD) over several months. Pathologically HIVAN is predominantly a glomerular disease, with “collapsing” glomerulopathy, focal and segmental glomerulosclerosis, variable interstitial inflammation, and tubular atrophy. It is not uniformly distributed among the HIV infected population, those of black race being disproportionately affected. Early reports of an appalling prognosis with or without dialysis are being countered by recent reports of encouraging responses to antiretroviral drugs and corticosteroids. Increasingly, other primary renal diseases are being described in HIV infected patients including, IgA nephropathy, an immune complex lupus-like nephropathy, and tubulointerstitial nephritis which carry widely differing prognoses.

Published series describing the range of renal disease seen in HIV infected patients are mainly from the United States and France, where the demographic characteristics of the HIV infected population are different from the United Kingdom, with a higher proportion of intravenous drug users and people of black racial origin. Other reports are composites from multiple centres or originate from tertiary renal referral centres. There is little published data from the United Kingdom. In this study we describe the presentation, pathology, and outcome of biopsy proved HIV associated renal disease seen at a specialist centre for HIV/AIDS in central London over a 4 year period.

Methods

We retrospectively reviewed the computerised database and necropsy records of the histopathology department of University College London Hospitals, from May 1992 to April 1996 in order to identify all HIV positive patients admitted to the specialist HIV/AIDS inpatient unit who underwent percutaneous renal biopsy. Investigation of renal disease or who were found to have renal disease at postmortem examination. During the period of
the study a median of 1123 HIV positive patients per year were seen in the outpatients’ department; of these patients 80% were white, 16.7% were black African or Afro-Caribbean, 1.5% were Indian or Asian, and 1.8% “others”. Over the same time period there were 438 new diagnoses of AIDS.

By reviewing the hospital case notes of these patients details of their age, sex, ethnicity, and risk factor for HIV infection were obtained. In addition, note was made of the known duration of HIV infection, CDC stage, and CD4 lymphocyte count at the time of diagnosis of renal disease. The mode of presentation of renal disease, drug therapy, specific renal interventions, and outcome were recorded. Cross reference was made to other HIV units in London in order to exclude the possibility that patients from our unit had presented to other units with renal failure. This revealed that two patients in the present study have previously been described in a pan-London study of HIV associated renal disease.17

Percutaneous renal biopsies were performed under ultrasound guidance using a true cut biopsy needle. All renal biopsy material was reviewed by one of us (MHG) a histopathologist experienced in interpretation of percutaneous renal biopsy and postmortem renal tissue. Indications for renal biopsy included presentation with (a) proteinuria with or without chronic renal failure and (b) acute renal failure, with or without proteinuria, where the cause remained uncertain after correction of fluid and electrolyte and acid base balance, withdrawal of nephrotoxic drugs, and treatment of intercurrent sepsis. Patients presenting during the study period with renal failure attributable

<table>
<thead>
<tr>
<th>Patient No/diagnosis</th>
<th>Presentation of renal disease</th>
<th>Specific interventions</th>
<th>Outcome of renal function</th>
<th>Survival (months): Cause of death</th>
</tr>
</thead>
</table>

### Renal biopsy:

1. **HIVAN**
   - ARF, Ccr = 28 ml/min, proteinuria = 3.0 g/24 h
   - Corticosteroids, ACE
   - Renal function stable, Ccr = 38 ml/min
   - 14: P. aeruginosa sepsicaemia

2. **HIVAN**
   - ARF
   - HD, corticosteroids
   - Deteriorated
   - 0: ARF

3. **HIVAN**
   - ARF, Ccr = 3 ml/min, proteinuria = 3.4 g/24 h
   - HD then CAPD
   - Maintenance CAPD
   - 3: P. aeruginosa peritonitis

4. **HIVAN**
   - ARF, Ccr = 1 ml/min, proteinuria = 10.5 g/24 h
   - HD then CAPD
   - Maintenance CAPD
   - 31: HIV wasting

5. **HIVAN**
   - ARF, Ccr = 18 ml/min, proteinuria = 9.3 g/24 h
   - CAPD
   - Maintenance CAPD
   - 6: CRF

6. **HIVAN**
   - CRF, Ccr = 70 ml/min, proteinuria = 10.0 g/24 h
   - None
   - CRF
   - 6: HADC, CRF

7. **HIVAN**
   - CRF, Ccr = 51 ml/min, proteinuria = 0.95 g/24 h
   - None
   - Slow decline in renal function, Ccr = 27 ml/min
   - 14: Alive

8. **Memb GN**
   - Proteinuria = 7.7 g/24 h, Ccr = 78 ml/min
   - ACE
   - Renal function stable, proteinuria controlled
   - 22: HIV wasting

9. **Memb GN**
   - CRF, Ccr = 53 ml/min, proteinuria = 15.8 g/24 h
   - ACE, corticosteroids
   - Slow decline in renal function. Creat = 254 µmol/1
   - 36: Alive

10. **Memb GN**
    - Proteinuria = 1.6 g/24 h
    - ACE
    - Normal renal function, proteinuria controlled
    - 46: Alive

11. **Memb GN**
    - CRF, Ccr = 38 ml/min, proteinuria = 0.53 g/24 h
    - ACE
    - Forced alkaline diuresis. Corticosteroids, withdrawal of all other drugs
    - Normal renal function
    - 1: HADC

12. **Rhabdomyolysis**
    - CRF, Creat = 600 µmol/l, CK = 600 000 IU/l
    - ACE
    - Forced alkaline diuresis
    - Normal renal function
    - 21: Alive

13. **Int nephritis**
    - CRF, Creat = 601 µmol/l, fever and loin pain
    - ACE
    - Normal renal function
    - 12: CMV encephalitis

### Necropsy:

14. **IGA nephropathy**
    - ARF
    - None
    - ARF
    - 0: PCC

15. **Memb-prolif GN**
    - ARF, anemia, thrombocytopenia, hypertension
    - None
    - Stable CRF
    - 0: disseminated CMV

16. **HUS**
    - ARF, anaemia, thrombocytopenia, hypertension
    - FFH, HD, blood transfusion
    - ARF
    - 0: HUS

17. **HUS**
    - ARF, anaemia, thrombocytopenia
    - FFH, blood transfusion
    - ARF
    - 0: HUS

**Notes:**

- ARF = acute renal failure; CRF = chronic renal failure; CAPD = chronic ambulatory peritoneal dialysis; HD = haemodialysis; ACE = angiotensin converting enzyme inhibitor; FFP = fresh frozen plasma; PCP = Pneumocystis carinii pneumonia; Ccr = creatinine clearance; HUS = haemolytic uraemic syndrome; HADC = HIV associated dementia complex; CK = creatine kinase; Creat = serum creatinine.
Results

Seventeen patients were identified, 13 had undergone ante-mortem renal biopsy and four had necropsy. A spectrum of renal disease was seen, the majority being due to primary intrarenal pathology rather than secondary to extrarenal events (table 1).

The demographics of the group were strikingly different from the general clinic population: of the 17 patients, eight (47%) were black African or Afro-Caribbean in origin, four were women, and of the 13 men six (46%) were heterosexual (table 1). Over 90% of patients presented with renal disease at an advanced stage of HIV infection, which was reflected in the low median CD4 count of 40 $\times$ 10$^6$/l (range 10–550 $\times$ 10$^6$/l). In six (35%) patients this was the first presentation of HIV disease.

Renal disease occurred at a rate of 0.36 per 100 patient years in the HIV clinic population. During this period 800 biopsies were performed at UCL Hospitals; thus, renal biopsies in HIV infected patients represented 1.6% of the workload.

The most frequent clinical presentation was with acute renal failure (ARF) which occurred in 10 (59%) patients. The remainder presented with proteinuria with or without chronic renal failure (table 2). Although the majority of patients (9/13) diagnosed in life subsequently died, only three deaths were directly attributable to renal disease, the others died from unrelated HIV conditions, reflecting their advanced HIV disease (table 2).

HIVAN was diagnosed in seven (41%) cases, all were of black racial origin and none was an IVDU (table 1). Renal ultrasound appearances were similar in patients with HIVAN and with other pathologies, showing normal or increased size; all but four scans showed increased echogenicity. The outcome in patients with HIVAN was variable. Of the four treated with acute haemodialysis, three survived and were maintained on continuous ambulatory peritoneal dialysis (table 2). High dose corticosteroids were used in two patients, one (case 2) did not survive the acute illness, the other (case 1) was diagnosed before development of end stage renal disease (ESRD). Despite florid changes on the biopsy (fig 1) stabilisation of the serum creatinine was achieved and maintained for 14 months, until death. Despite refusing treatment case 7 remained alive 14 months after diagnosis with only a minor decline in renal function. Median survival in patients with HIVAN was 10 months (range 0–31 months); 1 and 2 year survival rates 43% and 14% respectively.

Four patients (23.5%) had membranous glomerulonephritis (fig 2) only one was an IVDU and one had coexisting hepatitis B infection (table 1). Proteinuria was successfully controlled by angiotensin converting enzyme (ACE) inhibitors in all four cases. The 1 and 2 year survival in patients with membranous glomerulonephritis was 75% and 50% respectively—median survival 29 months (range 1–46 months).

Of those patients with other diagnoses, patient 3 developed ARF 3 days after commencing intravenous foscarnet and intravenous high dose aciclovir for varicella zoster induced acute retinal necrosis. Simultaneously, he received procaine penicillin with probenecid for latent syphilis. Renal biopsy showed interstitial nephritis typical of a drug reaction. Patient 14 who had IgA nephropathy, and had
presented with fulminant *Pneumocystis carinii* pneumonia and ARF, had no macroscopic or microscopic haematuria. Patients 16 and 17 with haemolytic uraemia syndrome had presentations typical of this syndrome (table 2). These cases have been described in detail elsewhere.18

**Discussion**

In this study we sought to describe the presentation, pathology, and outcome of renal disease seen in a central London specialist HIV/AIDS unit. During the 4 year period of the study we identified only 17 patients with renal disease who had undergone renal biopsy or necropsy. This may not reflect the true frequency of renal disease in patients at this centre, as only those undergoing a biopsy are included. There may be various reasons why biopsies were not performed in other patients—for example, in those with very advanced HIV disease, where further intervention was not felt to be appropriate, or it may reflect a reluctance on the part of physicians to perform an invasive procedure to diagnose a condition (HIVAN) thought from early reports to have a dismal prognosis.

The frequency of renal disease in HIV infected patients is difficult to estimate as HIVAN and other HIV associated renal pathologies are not classified as AIDS defining events and are therefore not reportable. However, necropsy studies and clinical/renal biopsy based series from the United States suggest a frequency of between 3% and 7%. The US Renal Data system has reported an increasing incidence of HIVAN since 1989. HIV associated ESRD currently accounts for 0.5% of all ESRD, and is overall the sixth commonest cause of ESRD in United States.19 It is estimated that by the end of the decade it will have become the third commonest cause in patients between the ages of 20 and 64 years. The prevalence among the United Kingdom HIV population is unknown. At UCL Hospitals the commonest cause of ESRD is “end stage” kidney/unclassified (27%); glomerulonephritis (14%) and diabetes mellitus (13.5%) are the second and third commonest causes respectively. HIV associated causes are ranked 14th and account for 1% of ESRD.

In our study HIVAN was the commonest renal disease identified, accounting for 41% of cases, all were of black racial origin. Studies from the United States and France also show this preponderance of cases among those of black race4 6 13 15 (table 3); thus, our observations are not unique. In contrast with these studies none of our patients with HIVAN were IVDU who have accounted for over 50% of cases in these series. IVDU are also at risk of developing heroin associated nephropathy (HAN) which has a similar histological appearance but a more benign prognosis.20

The reason for the racial predilection of HIVAN is unknown. However, the occurrence of glomerulosclerosis in other conditions such as diabetes mellitus, hypertension, HAN, and idiopathic focal segmental glomerulosclerosis in people of black race has been well described.1 This racial difference probably accounts for the low incidence of HIVAN so far reported from Europe, with the exception of France, as the proportion of their HIV population who are non-white is generally low. A recent report from Italy of 26 patients with biopsy proved renal disease found no cases of HIVAN, all were native Italians (table 3).21 Given the changing epidemiology of HIV infection in the United Kingdom, particularly in London, with an increasing number of HIV

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**Figure 2** Membranous glomerulonephritis (patient 8). High power view of a glomerulus stained with silver methenamine showing silver spikes on the epithelial side of the glomerular basement membrane.
infected Africans and Afro-Caribbeans accessing HIV services, it is likely that in future a greater number of cases of HIVAN will present to specialist centres, with a consequent need for appropriate planning of resources. HIVAN has been reported as occurring throughout the spectrum of HIV disease, although just over half of patients have a prior AIDS diagnosis at presentation. In contrast, as in our study, HIVAN may be the first manifestation of HIV infection, with patients presenting to services other than HIV units— the finding of focal segmental glomerulosclerosis on renal biopsy prompting counselling and HIV testing.

As HIVAN results in rapid loss of renal function presentation with ARF is common, although just over half of patients have a prior AIDS diagnosis at presentation. In our study, HIVAN may be the first manifestation of HIV infection, with patients presenting to services other than HIV units—the finding of focal segmental glomerulosclerosis on renal biopsy prompting counselling and HIV testing.

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### Table 3 Studies of renal disease in patients with HIV infection

<table>
<thead>
<tr>
<th>Country/location</th>
<th>Single or multicentre</th>
<th>Patient inclusion criteria</th>
<th>No of patients (No with biopsy/ncropy)</th>
<th>Patient characteristics</th>
<th>Renal tissue diagnoses</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA/New York</td>
<td>Single</td>
<td>Clinical*</td>
<td>55 (30)</td>
<td>49 M: 6; all black, 55% IVDU, 18% Hom</td>
<td>HIVAN 90%, mesangial GN 10%</td>
<td>15</td>
</tr>
<tr>
<td>USA/San Francisco</td>
<td>Single</td>
<td>Clinical*</td>
<td>27 (11)</td>
<td>26 M: 1, 17 black; 10 white, 48% IVDU, 44% Hom</td>
<td>HIVAN 27%, proliferative GN 27%, interstitial fibrosis 9%, IgG/M nephropathy 9%; other 28%</td>
<td>14</td>
</tr>
<tr>
<td>France/Paris</td>
<td>Multiple</td>
<td>Renal biopsy</td>
<td>60 (60)</td>
<td>51 M: 9; 29 black; 31 white, 41.5% Hom; 21.5% Het</td>
<td>HIVAN 43%; IC GN 37% &quot;lupus-like&quot; nephritis 16%, HUS 11.5%</td>
<td>13</td>
</tr>
<tr>
<td>Italy/Milan/Turin/Bologna</td>
<td>Multiple</td>
<td>Renal biopsy</td>
<td>26 (26)</td>
<td>21 M: 5; all white, 73% IVDU, 7.5% Hom, 7.5% Het</td>
<td>IC GN 65.5%, mesangioliprofibrative GN 15.5%, &quot;lupus-like&quot; nephritis 11.5%; minimal change GN 7.5%</td>
<td>21</td>
</tr>
<tr>
<td>UK/London</td>
<td>Multiple +</td>
<td>Current study†</td>
<td>34 (34)</td>
<td>25 M: 9 F; 19 black; 14 white; 1 Asian, 56% Hom, 38% Het; 6% IVDU</td>
<td>HIVAN 50%, membranous GN 14.5%, membranoproliferative GN 5%; HUS 12.0%; IC GN 3%; other 14.5%</td>
<td>17</td>
</tr>
</tbody>
</table>

*Clinical criteria = presentation with nephrotic syndrome or with renal failure with or without proteinuria; †some patients had >1 diagnosis; ‡two patients in current study previously reported in pan-London multicentre study.\(^{14}\); IVDU = IV drug user; Hom = homosexual; Het = heterosexual; HIVAN = HIV associated nephropathy; GN = glomerulonephritis; IC = immune complex; HUS = haemolytic uraemic syndrome.

ESRD in a mean of 8 weeks.\(^{7}\) The antiretroviral effects of zidovudine monotherapy are now known to be shortlived, and it may be that highly active combination antiretroviral therapy will have a greater impact on the clinical course of HIVAN. Glucocorticoids have also been shown to ameliorate the course of HIVAN and to reduce proteinuria. In a prospective study 20 consecutive patients with HIVAN were given oral prednisolone 60 mg/day for 2–11 weeks. Seventeen of 19 patients responded with improvements in serum creatinine. Of 13 patients who had estimations of urinary protein excretion 12 showed reductions.\(^{9}\) We successfully used prednisolone, in a similar regimen in one of our patients who had stable renal function for 14 months, until death. ACE inhibitors reduce proteinuria and slow progression of renal disease in patients with diabetic nephropathy, sickle cell renal disease, and non-diabetic renal disease, and have been shown to reduce proteinuria and stabilise creatinine in small numbers of HIV infected patients.\(^{15–20}\) In our study ACE inhibitors successfully reduced proteinuria in all the cases in which they were used.

Membranous glomerulonephritis has not been directly associated with HIV but infections such as hepatitis B are a well recognised cause. One of our cases was a hepatitis B eAg carrier and one had natural immunity but two did not have hepatitis B infection. The prognosis in published series is very variable with up to 30% developing progressive renal failure, some responding to corticosteroids or immunosuppressive agents such as chlorambucil. The prognosis in HIV infected patients is not known.

In conclusion, the commonest pathologies in this group of patients were HIVAN and membranous glomerulonephritis. Presentation in acute renal failure was common in patients with HIVAN. Renal ultrasound was not helpful in distinguishing this from other causes, underscoring the importance of renal biopsy for diagnosis. HIVAN occurred exclusively in those of African or Afro-Caribbean origin. It is likely that this presentation may be seen more frequently in the United Kingdom as the characteristics of the HIV epidemic evolve. As these
patients tend to present late in their disease. Nephrologists need to be aware of the possibility of HIV infection in those presenting with unexplained proteinuria or renal failure as this may be the first manifestation of HIV disease. Glucocorticoids and antiretroviral agents are emerging as effective treatments for HIVAN and earlier diagnosis before the development of ESRD may delay progression and obviate the need for the use of expensive dialysis resources.

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