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Renal pathology and premortem clinical presentation of Caucasian patients with AIDS: An autopsy study from the era prior to antiretroviral therapy

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Summary

Principles: Renal disease in patients with HIV infection is becoming increasingly frequent. A particular form of HIV-associated nephropathy (HIVAN) has been found in patients of predominantly African-American and Hispanic origin. However, only limited data are available on renal pathology and premortem clinical presentation of kidney disease in Caucasian patients with AIDS.

Methods: To determine the prevalence, clinical presentation and aetiology of renal disease in Caucasian patients with AIDS at the time of death we have performed a prospective autopsy study with 239 patients who died of AIDS between 1981 and 1989. None of these patients had received HIV-specific antiretroviral therapy. Autopsies and histological analyses were performed on the basis of a standardised protocol. Clinical and laboratory data were gathered according to a uniform questionnaire.

Results: 95% of patients were of Caucasian race. 75% of all patients had extended AIDS (stage IV). Clinical signs of nephropathy prior to death were found in 36% of patients, including proteinuria (18%), abnormal urinary sediment (19.5%), and renal insufficiency (11%). Histopathological lesions were present in 43% of the autopsies, with two or more distinct structural lesions in 12.5% of patients. Of the pathological findings 28% were glomerular or vascular, 33% were non-glomerular, and 29% were combined lesions. The remaining 10% were renal infiltrations of infectious agents or neoplastic tissue. The most common findings were ischaemic changes and vascular scars (18% of patients), as well as pyelo- and interstitial nephritides (12.2%). Importantly, FSGS was present in only 1.7% of patients, and only a single African patient had classical HIVAN.

Conclusions: Renal involvement in HIV disease is very common at the time of death among patients of Caucasian origin. However, classical HIV-associated nephropathy is absent in this population. These findings suggest that kidney disease affects all races and supports the hypothesis that HIVAN is specifically related to non-Caucasian ethnicity. The results reflect renal disease unaffected by HIV-specific antiretroviral therapy.

Introduction

Over the last few years physicians as well as pathologists have become aware of increasing involvement of the kidney in the acquired immunodeficiency syndrome (AIDS) [1]. This development can be explained by prolonged survival thanks to improved treatment, resulting in increased long-term complications from the underlying disease. From the clinical viewpoint renal problems in HIV disease are relatively common and are usually manifested as episodes of acute renal failure [2]. Nevertheless, a growing percentage of HIV-positive patients develop chronic renal insufficiency and, sooner or later, become candidates for chronic renal replacement therapy. Despite many years of research, some questions regarding kidney disease and HIV infection still remain unsolved. First, the clinical and histological spectrum of renal disease in Caucasians is not well determined. Second, it is unclear whether more specific therapies directed against the HIV virus may also affect renal disease. Several studies have investigated the underlying pathology in diseased kidneys from patients with AIDS. In the first small series of patients published in 1983 a broad spectrum of glomerular and non-glomerular lesions in kidneys of AIDS patients with proteinuria

or renal insufficiency was described [3]. In the same year, Rao et al. reported a distinctive pattern of sclerosing glomerulopathy which was termed HIV-associated nephropathy or HIVAN [4]. However, this unique form of nephropathy was later found to be predominant in African-American males and IV drug abusers. Three other larger series of deceased AIDS patients (36 from San Francisco and 56 and 30 from New York) were published consecutively in the mid- to late-eighties [5–7]. To our knowledge only three European autopsy studies have so far described renal pathology in HIV infected patients. Of these, two comprise data of mainly Hispanic [8] or African [9] patients respectively. An Italian group has published data of 120 Caucasian patients with HIV infection who died between 1989 and 1991 [10]. Unfortunately, clinical data on these patients are scant and no information on medical therapy was available. Many of these patients may have undergone treatment with HIV-specific antiretroviral therapy with AZT, which became available in the late eighties, and thus the course of their kidney disease may have been affected by antiretroviral treatment. Taken together, the natural history of kidney disease in Caucasians with AIDS is, with respect to clinical presentation and underlying pathology, still obscure. Knowledge of these topics is of importance for the clinical management of renal problems in patients with AIDS. Our study reports on the prevalence, clinical presentation and aetiology of renal involvement in Caucasian patients dying of AIDS in the era prior to antiretroviral therapy.

Methods

In a national Swiss cooperative study autopsies were performed prospectively in 239 consecutive patients who had died of AIDS between April 1981 and August 1989 at a number of institutions in Switzerland. Epidemiological, clinical, laboratory and autopsy data were gathered by the local investigators on the basis of a uniform questionnaire. The questionnaire covered the following information: age and sex of the patient; autopsy date; risk factors such as IV drug abuse, homo-, bisexual or promiscuous activity, blood transfusion (including vertical transmission from mother to child); ethnicity; date of HIV or AIDS diagnosis; date of first clinical signs of AIDS; serological status (antibody positivity) for HIV, CMV, toxoplasmosis, HSV, EBV and other viral or infectious agents; bacteriological analyses including blood, urinary and CSF cultures; clinical information (at time of death, or from a previous hospitalisation if available) on blood pressure, serum creatinine, proteinuria, urinary erythrocyte and leukocyte count by dipstick analysis, urinary sediment and bacterial culture. HIV disease was staged as proposed in 1987 by the Centers of Disease Control [11]. The questionnaire was analysed by the study coordinators. Despite systematic data collection with largely complete records, the available clinical information may not have been adequate to distinguish acute from chronic renal disease in every case. Assessment of renal function was based on serum creatinine measurements. Proteinuria was diagnosed from either positive urinary dipstick analysis and/or an abnormal protein amount in 24-hour urine collections (>0.5 g per day). If available, clinical information was used to distinguish between an acute and chronic course of proteinuria. Diagnosis of erythrocyturia and leucocyturia was based on dipstick analyses, and, if available, on microscopic examination of urinary sediments (positive if >0–4 erythrocytes and/or leucocytes per high power field (× 400 magnification); or any detectable erythrocyte- and/or leucocyte-cylinder[s]). In most instances, urinary cultures were obtained from patients with suspected urinary tract infection. Moreover, clinical aspects as well as autopsy and histological exams were taken into account to either confirm or rule out the possibility of acute urinary tract infection. All autopsies were performed within 12–24 h post mortem to minimize autolytic changes. Histological analyses were performed on the basis of a standardised protocol by at least two of the three renal pathologists (SH, MM and HB). Both kidneys of each patient were evaluated macroscopically and then processed histologically by routine haematoxylin and eosin stains as well as special staining procedures (PAS, PASM, mucicarmine and Congo red).

Results

Epidemiological characteristics

We analysed 239 consecutive autopsies of AIDS patients performed between April 1981 and August 1989. At the time of death all patients were residents of Switzerland and most were Swiss citizens. A total of 32 patients were originally from other European countries, Africa and the Americas. Except for six Africans and five Hispanics, all patients were of Caucasian race. 195 patients (82%) were male. The mean age at death was 39.25 ± 13.23 years. Identifiable risk factors for HIV virus acquisition were sexual contact (143 patients), IV drug use (59), blood transfusion (5) and maternal transmission at birth (2). According to the CDC definition published in 1987, a total of 180 patients (75%) suffered from extended

AIDS (stage IV). Of these, 146 patients had opportunistic infections (stage IVC) with one or more species of protozoa (164 diagnoses), fungi (177), viruses (271), bacteria (79), or tuberculosis (19). Another 48 patients had one or more AIDS-defining malignancies (stage IVD: 50 Kaposi sarcomas, 31 lymphomas). No obvious correlation between the stage of HIV infection and prevalence or type of renal involvement could be determined.

Clinical findings

The clinical findings associated with renal disease are summarised in Table 1. About a third of the patients had at least one clinical sign of nephropathy at the time of death (87 patients, 36%). It is interesting to note that proteinuria was the most common finding and the one most frequently detected in combination with other urinary abnormalities. Proteinuria was particularly prevalent in patients with tubulointerstitial lesions (10 of 40 patients, 25%), whereas only 13% of all glomerular and vascular changes were associated with proteinuria. However, two of the four patients with focal segmental glomerulosclerosis (FSGS) were proteinuric, in contrast to only 4 out of 17 patients (23%) with glomerulosclerosis unrelated to FSGS. Interestingly, proteinuria was found in 35% of patients with combined glomerular/vascular and tubulointerstitial renal pathology. Taken together, except for FSGS, tubulointerstitial damage in particular appears to predispose to abnormal renal protein excretion, probably because of tubular dysfunction with impaired protein reabsorption. "Non-specific" proteinuria was detected in 18% of patients without abnormalities in renal histology. Unlike proteinuria, erythrocyturia was much less frequent and, surprisingly, was found almost exclusively in patients without renal pathology. Moreover, erythrocyturia did not occur in a relevant percentage along with other abnormal urinary findings, nor was it predictive of renal insufficiency. These findings suggest that erythrocyturia is not very indicative of parenchymatous kidney disease but probably rather reflects post-renal pathology. Finally, leucocyturia was found mainly in patients with non-glomerular/inflammatory pathology alone or in combination with glomerular/vascular lesions.

Table 1
Clinical findings.

	No. (%)	Proteinuria No. (%)	Erythrocyturia No. (%)	Leucocyturia No. (%)	S-Creatinine ↑ No. (%)
Proteinuria	44 (18)	—	1 (2.3)	15 (34)	13 (29)
Erythrocyturia	26 (11)	1 (3.8)	—	1 (3.8)	1 (3.8)
Leucocyturia	20 (8.5)	15 (75)	1 (5)	—	7 (35)
S-Creatinine ↑	27 (11)	13 (48)	1 (3.7)	7 (26)	—

The table indicates absolute numbers and percentages (in parentheses) of patients with (a) given finding(s). The numbers in the first column relate to the findings listed vertically (percentages relative to entire study population). The remaining columns indicate numbers of patients with combined findings listed in the respective column and line (percentages relative to number in the first column). S-creatinine↑ indicates an increase in serum creatinine. All parameters were determined at the time of hospitalisation before death.

Table 2

Glomerular and vascular findings	No. of patients (%)
Glomerulosclerosis	17 (7)
FSGS	4 (1.7)
Other glomerulopathies	2 (0.8)
Ischemic changes (vascular scars)	35 (18)
Vascular thrombosis	1 (0.4)
Thrombotic microangiopathy	6 (2.5)
DIC	1 (0.4)
Non-glomerular findings	
Interstitial nephritis	14 (5.9)
Pyelonephritis	15 (6.3)
Other inflammatory changes, unspecified	8 (3.4)
Tubular necrosis	3 (1.3)
Papillary necrosis	1 (0.4)
Nephrocalcinosis	15 (6.3)
Interstitial fibrosis	2 (0.8)
Lymphoma	6 (2.5)
Infiltration with Kaposi's sarcoma	1 (0.4)
Tubulointerstitial involvement by:	
CMV	2 (0.8)
Cryptococci	1 (0.4)
miliar tuberculosis	2 (0.8)
tuberculous granulomas	1 (0.4)
acid-fast bacilli	1 (0.4)

Renal pathology

The renal pathology findings are shown in Table 2. Among all 237 patients investigated, 102 had a nephropathological finding at autopsy. Table 3 summarises the number of patients and diagnoses, listed by category and number of findings per patient. The prevalence of non-glomerular nephropathies was slightly higher compared to that of glomerular lesions: both the number of patients and the number of findings were higher in the category of non-glomerular lesions. In both categories, glomerular and non-glomerular, most patients had only one structural anomaly. Approximately one-third of the diseased kidneys had lesions affecting both glomerular and non-glomerular structures. The most frequent histological diagnosis was ischaemic nephropathy, which was

Table 3
Number of patients with nephropathological findings; listed by number and type of finding.

No. of findings	Glomerular/ vascular	Non-glomerular/ inflammatory	Either	Neoplastic infectious	No. of patients	No. of findings
Single	24 (10)	34 (14)	—	14 (5.9)	72 (30)	72 (52)
Double	7 (2.9)	6 (2.5)	11 (4.6)	0	24 (10)	48 (35)
Triple	0	0	6	0	6 (2.5)	18 (13)
No. of patients	31 (13)	40 (17)	17 (7.2)	14 (5.9)	102 (43)	—
No. of findings	38 (28)	46 (33)	40 (29)	14 (10)	—	138 (100)

Percentages are given between parentheses respective to a total of 237 patients or a total of 138 findings

chiefly based on scarring related to vascular lesions. Sclerosis of the glomeruli was noted in some 7% of patients. Only four were diagnosed with focal segmental glomerulosclerosis. Interestingly, only one among these showed the typical renal findings of collapsing FSGS, which has also been termed HIV-associated nephropathy (HIVAN). Collapsing FSGS involves global rather than focal sclerosis of a collapsed glomerular tuft together with severe tubular injury, proliferative microcyst formation and tubular degeneration. This entity has been found to be chiefly prevalent in patients of African or African-American origin. Not surprisingly, the one patient in our series with the collapsing form of FSGS was also African. Among the remaining histopathological diagnoses, nonspecific interstitial changes and pyelonephritides predominated. A relatively large number of patients had nephrocalcinosis, with a prevalence identical to that of the pyelonephritides. It is of particular interest that none of these patients had received amphotericin B, which is known to cause nephrocalcinosis [12]. Secondary infiltration of the kidney with neoplastic tissue, particularly lymphoma, was found in approximately 3% of the autopsies. Similarly, tubulointerstitial involvement due to infectious agents was noted in another 3% of kidneys.

Discussion

Based on 239 consecutive autopsies performed in Switzerland between 1981 and 1989 we have analysed renal involvement in patients dying of AIDS. As far as we know this is the largest series of this kind ever published. The vast majority of patients were of Caucasian race: this is in contrast with most other analyses – mainly performed in the United States but also in Europe – whose patient populations largely consisted of a broad ethnic mix of Caucasians, African-Americans [9] and Hispanics [8]. Moreover, none of the patients in our analysis had been on HIV-specific antiretroviral therapy. Thus, our study is well suited to determining the prevalence and spectrum of kidney disease associated with HIV infection in a Caucasian population unaffected by treatment of the underlying disease.

Except for race, our patient population was highly comparable with other published series as far as age, sex and risk factors for acquiring AIDS were concerned. A majority of our patients (60%) had advanced HIV disease of stage IVC and IVD under the 1987 classification of the Centers of Disease Control [11]. No obvious correlation between the stage of HIV infection and prevalence or type of renal involvement could be determined in our study (data not shown). Mortality appears to be related chiefly to the stage of AIDS and not to the presence of nephropathy. Reflecting advanced HIV disease, a high percentage of our patients had disseminated neoplasias and/or infectious complications.

Renal insufficiency, defined as an increase in serum creatinine above normal, was found in 11% of patients in the present investigation. This is comparable with the 7.4% in a New York study [2]. However, with the clinical information available we could not always distinguish between acute and chronic renal function impairment in our study population. In our analysis, some patients had other clinical signs of nephropathy which were not always accompanied by renal insufficiency. 44 patients were proteinuric (18%), which is in the range described by others [13]. Proteinuria seems to be a good indicator of glomerulosclerosis and in particular FSGS. Moreover, tubulointerstitial pathology causing impaired protein reabsorption is obviously another frequent cause of proteinuria. In contrast, erythrocyturia was a poor indicator of renal disease. Among the 26 cases with a pathological urinary erythrocyte count, only one showed renal pathology at autopsy (nephrocalcinosis), whereas leucocyturia and proteinuria were found in 50 and 34% respectively of patients with renal pathology. Again, these findings need to be interpreted with caution because in some instances we were unsure about the preexistence of clinical signs. Thus, we cannot always rule out the possibility of acute rather than chronic presentation, and, accordingly, the findings may represent acute urinary tract infection or bleeding rather than specific chronic renal disease.

Among the 239 autopsies performed in the present investigation, we found pathological renal changes in 102 patients (43%). This prevalence appears to be slightly lower than that in other publications (see Table 4). For example, d'Agati et al. reported 69% of patients with renal pathology at

autopsy [7]. Similarly, in a Spanish investigation by Hernandez et al. there was a 59% published percentage for renal involvement among patients with HIV disease [8]. Monga et al. found a prevalence of 68% in their mainly Caucasian population of the late eighties [10]. As shown in Table 4, no apparent association exists between ethnicity and the occurrence of renal involvement. In contrast, the relative distribution between glomerular and non-glomerular renal disease varies substantially among different ethnic groups. While an autopsy study from the Columbia Presbyterian Medical Center described glomerular disease in only 5.2% of affected kidneys, a publication from Miami reports glomerular pathology in 100% of patients with renal pathology. Apparently the percentage of glomerular disease is determined mainly by the ratio of African-American and Hispanic to Caucasian patients. The former category of patients has a much higher prevalence of focal segmental glomerulosclerosis, chiefly in the appearance of classical HIV-associated nephropathy (HIVAN) [15]. This interdependence of race and FSGS has been demonstrated most strikingly in the French study by Nochy. Among their black patients, 79% had FSGS compared with only 6% in whites [9]. The patient cohort studied by the Italian group of Monga et al. between 1989 and 1991 bears the strongest resemblance to our own patient population as far as ethnicity is concerned. This cohort was found to have glomerular changes in 37% of diseased kidneys [10]. Our own study confirms the association of racial factors with histological findings. Glomerular and non-glomerular lesions were found with comparable frequency of about 30% each, but focal glomerular sclerosis was present in only four patients (1.7%). Of these four patients, only one showed the classical signs of collapsing FSGS typical of HIVAN. Characteristically, this particular patient was an African male originating from Zaire. Most of the glomerular lesions in our analysis were due to diffuse glomerulosclerosis and non-specific ischaemic changes, presenting mainly as vascular scarring. Finally, several patients presented with renal thrombotic microangiopathy, a finding compatible with haemolytic uraemic syndrome as described previously in association with AIDS [16].

Among the tubulointerstitial changes, the most frequent were pyelo- and interstitial nephritides, and nephrocalcinosis. Whereas the former can be related either to infectious or inflammatory processes due to HIV disease, it is more difficult to explain the high incidence of nephrocalcinosis. Interestingly, nephrocalcinosis has also been found by others with a frequency of up to 43% in patients with AIDS [7, 8]. Nephrocalcinosis has been attributed to amphotericin B treatment [12]. However, none of the patients with this finding in our study had received amphotericin B before. An interesting observation has been published by Bargman and co-workers, who found nephrocalcinosis associated with Pneumocystis carinii (PC) infection in a patient with acquired immunodeficiency syndrome. Calcifications occurred predominantly in areas of renal PC infection [17]. Although we did not specifically test for Pneumocystis carinii in our renal autopsy material, it is remarkable that 73% of our patients with nephrocalcinosis had a history of PC pneumonia. Conversely, PCP had occurred in only 42% of patients without nephrocalcinosis. This observation supports the notion that Pneumocystis carinii infection may trigger renal calcification in HIV-positive patients. The prevalence of serologies positive for cytomegalovirus infection was 37% in this study. Two of the patients in our analysis had renal tubulointerstitial cytomegalovirus involvement. All kidneys affected by tuberculosis were from patients with positive TB blood cultures, whereas 84% of TB-positive patients showed no renal involvement at autopsy. Finally, renal infiltration by neoplastic tissue was discovered in seven patients. The frequency of neoplastic renal infiltration in AIDS is therefore comparable with that found by other authors [13, 15]. Despite the high prevalence of Kaposi's sarcoma in our cohort, the kidney was involved in only 2% of these patients. In contrast, renal infiltration with lymphoproliferative tissue occurred in 19% of patients with lymphoma.

The prevalence of renal pathology in our study is high and the findings are miscellaneous, although vascular ischaemic and tubulointerstitial lesions are predominant. Nevertheless, one may argue that these changes simply reflect non-specific lesions in the kidney of a patient with chronic

Table 4

Studies investigating HIV associated renal disease.

Authors and year	Ref.	Place	No. of patients studied	Caucasians (%) [1]	Renal lesions (%)[1]	Glomerular alterations (%)[2]
Pardo et al.; 1987	14	Miami	135	22[3]	31	100
D'Agati et al.; 1989	7	New York	30	47	69	5.2
Seney et al.; 1990	13	Dallas	50	80	approx. 80	12
Nochy et al.; 1993	9	France	60	52	100[4]	69
Martinez et al.; 1996	8	Spain	85	—[5]	59	"few"
Monga et al.; 1997	10	Italy	120	100	68	37

[1] Percentage of all patients studied (unless stated otherwise).
[2] Percentage of all renal lesions.
[3] Percentage of patients with renal lesion.
[4] Only patients with clinical evidence of nephropathy were investigated.
[5] Patients from Spain only.

illness. As we did not incorporate a group of matched controls with patients who died of other chronic (infectious) diseases, we cannot rule out this possibility completely. However, our own experience and the literature do not suggest any other condition that causes renal disease with a frequency and pattern similar to that found in our AIDS patients.

In summary and conclusion, the present investigation has shown that renal involvement is highly prevalent among patients of mainly Caucasian origin who have died of AIDS without prior HIV-specific antiretroviral therapy. In contrast to other studies with a more diverse racial population, collapsing FSGS was almost absent in our cohort and was found only in a single black patient from Zaire. This finding corroborates the hypothesis that HIVAN is restricted almost exclusively to patients of African-American and Hispanic origin. Otherwise, our cohort presented with a broad spectrum of glomerular and non-glomerular pathologies very similar to that in other published series from the United States and other European countries. The mechanisms by which HIV infection causes renal disease remain to be elucidated. The kidney has recently been shown to be a site of HIV virus replication [18], and a direct effect of the virus on renal tissue has been suggested [19]. While our results reflect renal pathology induced by the HIV virus, further studies are needed to determine the influence of HIV-specific pharmacotherapy on the development and course of renal disease in AIDS patients.

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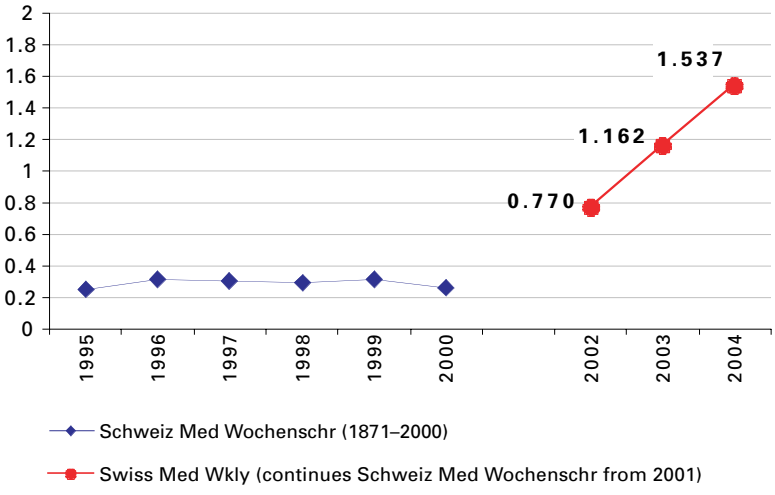

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