Original Article

The Histological Appearances of the Adult Kidney in HIV Infection at Autopsy at the University Teaching Hospital in Lusaka

AL Mucheleng'anga[1]*, C Kapenda[2], V Mudenda[3], C Marimo[1]

[1]*Department of Pathology and Microbiology, University of Zambia School of Medicine, Lusaka.*
[2]*Department of Physiotherapy, University of Zambia School of Medicine, Lusaka*
[3]*Department of Pathology and Microbiology, University Teaching Hospital, Lusaka.*

ABSTRACT

Background: Kidney disease in acquired immunodeficiency syndrome is very common. The cause of the various histological appearances include HIV infection of the kidney, immunologic responses to the virus, opportunistic infections, neoplasms and consequences of anti-retroviral therapy that characterize the acquired immunodeficiency virus (AIDS). There are no autopsy studies conducted in HIV-infected cases in sub-Saharan Africa on the histological lesions of the kidney.

Objective: To describe kidney histological appearances in HIV infection using autopsy material at the UTH, Lusaka.

Methods: A descriptive study of 200 paraffin blocked kidney autopsy tissue samples collected between 2010 and 2012 in the Zambia Neuro-AIDS study (Subtype C Neuro-AIDS and pathogenesis in Zambia) was conducted at the University Teaching hospital in Lusaka, Zambia. The study aimed at describing the histological appearances of the adult kidney in Human Immunodeficiency Virus infection.

The study population consisted of all HIV infected cases above the age of 16years that had been on anti-retroviral therapy and those that were not commenced. The decedents were unselected for the presence of overt kidney disease. Paraffin blocked kidney tissue samples were processed according to standard histopathology laboratory protocols at the University Teaching Hospital and examined at light microscopic level.

Results: Two hundred (200) cases were examined of which 128 cases were male and 72 were female. One hundred and sixty nine cases (84.5%) revealed renal lesions. The renal histopathological lesions included; tubulointerstitial 65%, glomerular 59%, vascular 2%, and 19.5 % of cases revealed renal tuberculosis. Fungal, viral infections and malignancies were not identified.

Conclusion: The investigation has shown that renal lesions are highly prevalent (84.5%) among HIV infected cases at the University Teaching Hospital.

INTRODUCTION

Kidney disease in Acquired Immunodeficiency Syndrome (AIDS) patients was described before human immunodeficiency virus (HIV) was demonstrated to be the causative agent in 1984 and since then many studies have provided evidence that the kidneys harbor histologically diverse lesions in HIV-infected cases.[1, 2, 3] Antiretroviral therapy (ART) in the treatment of HIV infection has reduced the mortality and morbidity rates among the HIV population; however prolonged use of ART is said to bring about alterations in lipid metabolism leading to an increase in the prevalence of secondary

*Corresponding author:
Dr. Luchenga Adam Mucheleng'anga
Zambia Police Service.
Forensic Sciences Laboratory.
P.O Box 50104
Email:Luchengam@gmail.com

Key Words: *Histological appearances, autopsy, HIV infected kidney*

diabetic and hypertensive kidney damage.[4,5] Furthermore antiretroviral drugs such as indinavir and tenofovir have been associated with nephrotoxic effects.[5]

The kidney is divided into four components (the glomeruli, tubules, interstitium and the blood vessels) for the purpose of histological description. HIV affects all the compartments and produces varied histological appearances.[6,7] Although the most common histologic lesion seen among HIV-infected patients is HIV-associated nephropathy (HIVAN) a spectrum of other kidney histologic lesions in HIV disease have been described.[2,3,4] The causes of the various histological appearances include; HIV infection of the kidney, immunologic responses to the virus, opportunistic infections, neoplasms and consequences of various therapies or hemodynamic derangements that characterize AIDS.[8] Literature review shows that all renal pathologies are seen in HIV infection in Europe and America however, there is no literature on autopsy studies conducted in sub-Saharan Africa.[9,10]

METHODS

This descriptive study investigated renal lesions of the adult kidney in HIV infected patients at the University Teaching Hospital in the period 2010 to 2012. Two hundred (200) paired blocked autopsy kidney samples were collected from the Zambia Neuro-AIDS study (subtype C neuro-AIDS and pathogenesis in Zambia) which was set up to investigate the effects of HIV on the brain at autopsy.

A review of available clinical data which included age, sex, past medical history, drug history, CD_4+ count results, urea, creatinine, proteinuria and clinical diagnosis was conducted. Tissue was processed according to the standard operating procedures at the University Teaching Hospital and microscopic examination to evaluate; glomerular, interstitial, tubular and vascular appearances was conducted.

Data was entered into Epi infor 7 and analyzed using the statistical software package SPSS version 21. Descriptive analytical statistics were used to provide simple summaries about kidney samples and descriptions thereof. Continuous variables were expressed as percentages and as actual numbers. Categorical variables were expressed as percentages. Descriptive statistics were shown by graphical representation. All statistical tests were at 5% significance level. The Pearson's chi-squared test was used for comparison of proportions between groups. The Fisher's exact test was used when one or more of the cells had an expected frequency of five or less. The Independent Samples T-test and Mann-Whitney U Test were used to compare means and medians, respectively. Selection for entry into logistic regression model was based on $P < 0.20$ or clinical significance. A waiver was granted by ERES Converge IRB.

RESULTS

Clinical, demographic characteristics and renal lesions

There were 200 decedents, 128 (64%) male and 72 (36%) female. The mean age was 35.6 ± 8.70 years. Categorically, there were 60 (30%) cases between the age 16 – 30 years, 120 (60%) between 31 – 45 years, 18 (9%) between 46 – 60 years, and 2 (1%) between 61 – 75 years.

One hundred and three cases (51.5%) had a diagnosis of TB medical ,8 (4%) had a clinical diagnosis of renal disease, 80 (40%) had other medical history, and 14 (7%) had no medical history.

There were 65 (32.5%) cases on ART and 135 (67.5%) cases not on ART . Out of the 65 cases on ART 63 cases had information of drug combinations. Thirty seven cases (58.7%) were on Truvada/EFV and 18 (28.6%) were on Atripla. Twenty nine (29) cases had CD4 count results; twenty three (23) cases had urea results, with median urea value of 5.1 Thirty nine (39) cases had creatinine results with median creatinine value of 90.1. Refer to Table 1.

At 5% significance level, none of the study variables were significantly associated with the presence of renal lesions. Refer to Table 2 .

Logistic regression analysis done for presence of renal lesions showed that cases on ART had on average 86% reduced odds for presence of renal lesions compared to cases not on ART [Odds Ratio (OR) = 0.14, 95% Confidence Interval (CI) = 0.06 – 0.34, $P < 0.001$). Cases with no TB infection had on average 69% reduced odds for presence of renal lesions (OR = 0.31, CI = 0.18 – 0.53, $P < 0.001$). Refer to table 3.

Table 1. Characteristics of the study cases

Variable	Frequency (n = 200)	
	n	%
Sex		
Female	72	36
Male	128	64
Age category		
16 - 30 years	60	30
31 - 45 years	120	60
46 - 60 years	18	9
61 - 75 years	2	1
Medical history		
TB	103	51.5
Renal Lesions	8	4
Other	80	40
None	14	7
ART History		
PreART	135	67.5
ART	65	32.5
Renal Lesions		
Present	169	84.5
Absent	31	15.5
Glomerular		
No	118	59
Yes	82	41
Tubules		
No	70	35
Yes	130	65
Blood vessels		
No	196	98
Yes	4	2
Interstitium		
No	85	42.5
Yes	115	57.5
TB infection		
Yes	39	19.5
No	161	80.5
Age (n, mean, SD)	200, 35.6, 8.70	
Urea (n, median, IQR)	23, 5.1, 40.1	
Creatinine (n, median, IQR)	39, 90.1, 81	

Table 2. Bivariate analysis for association with renal lesions

Variable	Renal Lesions Present		Renal Lesions Absent		P-value
	n	%	n	%	
Sex					
Female	62	36.7%	10	32.3%	0.64[c]
Male	107	63.3%	21	67.7%	
Age category					
16 - 30 years	51	30.2%	9	29.0%	0.99[f]
31 - 45 years	101	59.8%	19	61.3%	
46 - 75 years	17	10.1%	3	9.7%	
TB medical history					
No	79	46.7%	18	58.1%	0.25[c]
Yes	90	53.3%	13	41.9%	
Renal Lesions medical history					
No	162	95.9%	30	96.8%	0.99[f]
Yes	7	4.1%	1	3.2%	
Other medical history					
No	103	60.9%	17	54.8%	0.52[c]
Yes	66	39.1%	14	45.2%	
HAART History					
PreHAART	110	65.1%	25	80.6%	0.09[c]
HAART	59	34.9%	6	19.4%	
CD4 count					
0 - 100	11	47.8%	4	66.7%	0.65[f]
Above 100	12	52.2%	2	33.3%	
HAART Regimen					
Atripla	15	26.3%	3	50.0%	0.34[f]
Truvada	42	73.7%	3	50.0%	
TB infection					
Yes	36	21.3%	3	9.7%	0.13[c]
No	133	78.7%	28	90.3%	
Age (n, mean, SD)	169, 35.5, 8.89		31, 36.2, 7.65		0.68[t]
Urea (n, mean rank)	16, 13.2		7, 9.2		0.20[m]
Creatinine (n, mean rank)	32, 21.28		7, 14.14		0.14[m]

[c]=Chi Square Test, [t]=Independent samples T-test, [f]=Fisher's exact test, [m]=Mann-Whitney U test

Table 3. Logistic regression analysis predicting renal lesions

Variable	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	P-value
Drugs History			
Pre-HAART	1	1	
HAART	0.10 (0.04 - 0.24)	0.14 (0.06 - 0.34)	<0.001
TB Infection			
Yes	1	1	
No	0.23 (0.14 - 0.38)	0.31 (0.18 - 0.53)	<0.001

Renal lesion in the various compartments

Two hundred (200) cases were examined and 169 (84.5%) cases revealed renal lesions, and this proportional difference was significant (P<0.001). Tubulointerstitial lesions were most prevalent, 130 (65%) cases, glomerular lesions 118 (59%) cases, and 4 (2%) had vascular lesions. There was no neoplasm identified in the study population. There were 39 (19.5%) cases renal tuberculosis. Refer figure 1 and Table 2

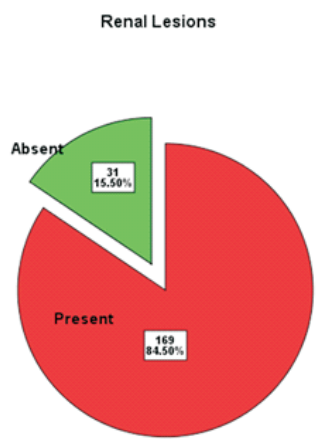

Figure 1. Renal lesions frequency pie chart

DISCUSSION

This study provided a window into the range of renal histological lesions seen in HIV-infected cases that were unselected for the presence of kidney disease at UTH in Lusaka. The study population consisted of two hundred (200) cases and 165 (84.5%) of cases revealed renal lesions, the cases being black Africans only.

Clinical and demographic characteristics

In this study sex, age, history of kidney diseases, level of CD4 count, level of urea and creatinine were not significantly associated with the presence of renal lesions. The findings are at variance with recent data from biopsies that show an association between age and renal lesions, however this difference is supported by the idea that clinical and autopsy kidney studies show different statistics for the same lesions.[11, 12]13

Kenneth *et al* in a population-based study stated that some of the predictors of renal disease among women with proteinuria included an absolute CD4 cell count of ⩽200 cells/µL [14]. This investigation shows a different result due to the population differences such as having both males and females and the fact that in our study the patients were unselected for kidney disease and their study was limited by its inability to define histologic lesions and may have included women with HIV-related renal diseases other than HIVAN [14].

Logistic regression done the absence of Tb clinically and HIV infected cases on ART in this study showed an association, and this is in line with studies conducted by Rule *et al*., and Tan *et al* [15, 12]. The findings are also supported by Quesada *et al*., who showed that several types of ART are associated with kidney dysfunction [16].

Light microscopy

This study provided a detailed histological description of the various compartments of the kidney in adults infected with HIV/AIDS at autopsy. One hundred and sixty-five cases showed renal lesions. This study compares very well with studies in literature as Wyatt *et al* . had a mixed population with blacks in their study.[17, 25]

One hundred and thirty (130) cases showed the tubulointerstitial group of lesions. The tubulointerstitial group was composed of the following lesions in order of frequency of lesions; tubular necrosis (79%), chronic inflammation (65%) and reparative changes (Figures 3 and 4) were among the predominant interstitial responses to injury. Acute inflammation, interstitial fibrosis, edema, interstitial necrosis, wrinkled basement membranes and tubular dilation were below 10%. Tubular necrosis in this study was caused by HIV infection of the epithelial cells in tubules .[19, 20] In comparison to quoted autopsy studies in literature, this study recorded a lower prevalence of tubulointerstitial lesions (84%).[17, 18, 22] This is due to the differences in sample sizes; this study had a high sample size. Most of the tubulointerstitial lesions found in this study represented renal disease that was not diagnosed clinically.

One hundred and eighteen (118) - 59% cases revealed glomerular lesions. The most prevalent lesion was extracapillary hypercellularity (81%) followed by global sclerosis at 54% (Figures 5 and 6). The causes of hypercellularity in the study were immune-mediated which were not acutely severe enough to cause crescent formation. Global sclerosis indicates and end-stage glomerulus.[20] This study compares relatively well to reviewed autopsy studies due the composition of the study populations i.e. mixed race population including blacks and Hispanics.[22, 23] Literature shows that glomerular lesions are less likely to occur in a black race population compared to the white population .[24] This investigation revealed that glomerular lesions are as prevalent in the black population .

In this study four cases showed a vascular reaction to injury. Two cases showed hyperplastic sclerosis and two showed intimal thickening. The hyperplastic sclerosis was caused by undiagnosed hypertension. Studies show black ethnicity is a strong and independent risk factor for peripheral arterial disease .[25] This is in contrast to the findings of this study and other autopsy studies, again underscoring the idea that clinical and autopsy studies in kidney pathology in HIV cases yields different results.[11, 17, 18, 22, 24, 25, 13]

This study revealed a 19.5% prevalence of renal TB infection (Figures 7 and 8) .This is because of the high number of decedents diagnosed with tuberculosis at the time of admission. No fungal organisms or changes consistent with viral infections were identified in this study. The kidney is a site of isolated infection or part of a systemic process.[22, 26]

HIV-associated nephropathy was not identified in this study. This is in contrast to the view that HIVAN is a common lesion in HIV cases as shown by a by Han *et al* .[27] The reason for the low prevalence of HIV-associated nephropathy in this study is that the cohort was unselected for the presence of kidney disease.

There were no neoplasms identified in this study showing that they are uncommon in the kidneys of HIV cases. This is in keeping with the low prevalence of neoplasms in literature. Autopsy studies reviewed in literature showed neoplasms such as Kaposi's sarcoma and lymphoma .[11, 18, 21, 22, 23, 24]

CONCLUSIONS AND RECOMMENDATIONS

The investigation has shown that renal lesions (tubulointerstitial 65%, glomerular 59%, vascular 2% and renal infections-TB-19.5%) are highly prevalent (84.5%) among cases at the UTH infected with HIV.

There are lesions like basement membrane thickening, podocyte foot effacement, light chain deposition disease, immune complex deposition etc. that are not apparent on light microscopy, so future studies with the use of immunofluorescence and electron microscopy are required to note and refine the presence of those lesions.

ACKNOWLEDGEMENT

Many thanks to Vanderbilt University, Ministry of Health for sponsoring this research and UTH for using their facility.

I am grateful to my wife and children for the support and encouragement.

REFERENCES

1. Bourgoignie J, Meneses R, Ortiz C, Jaffe D, Pardo V. The clinical spectrum of renal disease associated with human immunodeficiency virus. *Am J Kidney Dis*. 1988 Aug; 12(2):131-7.
2. Cohen S, Chawla L, Kimmel P. Acute kidney injury in patients with human immunodeficiency virus infection. *Curr Opin Crit Care*. 2008 Dec; 14(6):647-53.s
3. Varma P, Prasher P, Deshpande G. Spectrum of renal lesions in HIV patients. *J Assoc Physicians India* 2000; 48:1151.
4. Herman E, Klotman P (2003). HIV-associated nephropathy: epidemiology, pathogenesis, and treatment. *Semin Nephrol* 2003; 23(2): 200–208.
5. Adedeji T, Adedeji N, Adebisi S, Idowu A, Fawale M, Jimoh K. Prevalence and Pattern of Chronic Kidney Disease in Antiretroviral-Naive Patients with HIV/AIDS. *J Int Assoc Provid AIDS Care* 2015, 26:434-40.
6. Jennette J, Olson J, Schwartz M, Silva F. Primer on the Pathologic Diagnosis of Renal Disease in: Heptinstall's Pathology of the Kidney, 6th Edition, 2007, Chapter 3.
7. Agaba E, Agaba P, Sirisena N. Renal disease in the acquired immunodeficiency syndrome in north central Nigeria. *Niger J Med* 2003; 12:120.
8. D'Agati V, Suh J, Carbone L. The pathology of HIV nephropathy: A detailed morphologic and comparative study. *Kidney Int* 1989; 35:1358.
9. Winston J, Klotman M, Klotman P. (1995). HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection. *Kidney Int*; 55:1036-40.
10. D'Agati V, Appel G. HIV infection and the kidney. *J Am Soc Nephrol* 1997; 8(1): 138–152.
11. Monga G, Mazzucco G, Boldorini R, Cristina S. Renal changes in patients with acquired immunodeficiency syndrome: a post-mortem study on an unselected population in north western Italy. *Mod Pathol*. 1997 Mar; 10(3):159-67.
12. Tan JC, Busque S, Workeneh B, Ho B, Derby G, Blouch KL, et al. Effects of aging on glomerular function and number in living kidney donors. *Kidney Int*. 2010, 78:686-692.24.
13. Pollok R, Francis N, Cliff S. Kaposi's sarcoma in the kidney. *Int J STD AIDS* 1995; 6:289.
14. Kenneth H. Mayer, Section Editor and Lynda Anne Szczech. Renal Diseases Associated with Human Immunodeficiency Virus Infection: Epidemiology, Clinical Course, and Management. *Clin Infect Dis*. (2001) 33 (1): 115-119. doi: 10.1086
15. Rule A, Amer H, Cornell L, Taler S, Cosio F, Kremers WK *et al*., The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med*. 2010, 152:561-567.
16. Michael H, Veronica V, Julie O, Elena H, Matthew, Robert D, et al 2005 Ethnicity and Peripheral Arterial Disease, The San Diego Population Study. *Circulation*. 2005; 112:2703-2707
17. Martinez P, Pena J, Arnalich F, Garcia M, Adridano O, Gonzalez J, et al. Spectrum of the renal pathology in HIV infection: description of 85 autopsies and clinico-pathologic correlation. *Rev Clin Esp* 1996; 196(9):577–83.
18. Soriano-Rosas J, Avilla Carsado M , Carrera-Gonzalez E, Chavez-Mercado L, Cruz-Ortiz H . AIDS-associated nephropathy: 5-year retrospective morphologic analysis of 87 cases. *Pathology research and practice* 1998; Volume 194, Issue 8, 1998, Pages 567–570.
19. Madeddu G, Quirino T, Carradori S, Ricci E, Grosso C. Renal toxicity in HIV-infected patients receiving HAART including tenofovir. *Infec Med*. 2006 Sep; 14(3):125-34.
20. Vinay K, Abul K. Abbas J, Aster C. Robbins and Cotran, Pathologic basis of disease, ninth edition. Pages 903-910.ISBN 978-1-4557-2613-4. Elsevier Saunders, 1600 John Kennedy Blvd. Ste 1800 Philadelphia, PA 19103-2899
21. Quesada PR, Esteban LL, Garcia JR, Sanchez RV, Garcia TM, Alonso-Vega GG, et al. Incidence and risk factors for tenofovir-associated renal toxicity in HIV-infected patients. Int J Clin Pharm 2015, 26:26.21.
22. van der Reijden H, Schipper M, Danner S. Glomerular lesions and opportunistic infections of

the kidney in AIDS: An autopsy study of 47 cases. *Adv Exp Med Biol* 1989; 252:181.

23. Kurz M, Burkhalter F, Dickenmann M, Hopfer H, Mayr M, Elzi L, et al. Acute kidney injury KDIGO stage 2 to 3 in HIV-positive patients treated with cART–a case series over 11 years in a cohort of 1,153 patients. *Swiss Med Wkly*. 2015, 145:w14135.
24. Seife H, Marcel W, Hans-Rudolf B, Gieri C, Michael M. Renal pathology and premortem clinical presentation of Caucasian patients with AIDS: An autopsy study from the era prior to antiretroviral therapy. *Swiss Med Wkly* 2001; 131:412–41
25. Wyatt M, Susan M, Rebecca K, Mary E, Paul E. The spectrum of kidney disease in patients with AIDS in the era of antiretroviral therapy. *Kidney Int*. 2009 February; 75(4): 428–434.
26. Niedt G, Schinella R. Acquired immunodeficiency syndrome: Clinicopathologic study of 56 autopsies. *Arch Pathol Lab Med* 1985; 109:727.
27. Han T, Naicker S, Ramdial P, Assounga A. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int.* 2006 Jun; 69(12):2243-50 PubMed ID: 16672914.
28. Nochy D, Glotz D, Dosquet P. Renal lesions associated with human immunodeficiency virus infection: North American vs European experience. *Adv Nephrol Necker Hosp* 1993; 22:269.
29. D'Agati V, Appel G. Renal pathology of human immunodeficiency virus infection. *Semin Nephrol*. 1998 Jul; 18(4):406-21.