COMPARISON BETWEEN LUPUS NEPHRITIS IN HIV POSITIVE PATIENTS AND HIV ASSOCIATED IMMUNE COMPLEX GLOMERULONEPHRITIS WITH "LUPUS–LIKE" FEATURES: a clinico-pathologic study

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A research report submitted for the Degree of Master of Medicine at the Department of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand

TABLE OF CONTENTS

DECLARATION

I, Margaret Masala Mathaba (student number 692044), hereby declare that this research report is my work. It is submitted for the degree of Master of Medicine in the Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences at the University of the Witwatersrand.

DEDICATION:

I dedicate this research report to my dear husband for always supporting me, my beautiful children who always believe in me, my parents (#GiThudozwe#WhatALife) for their encouragement, and always believing in me.

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease seen commonly in black females of childbearing age. More than half of the patients present with renal disease or lupus nephritis complications. It has been reported in the literature that co-infection with HIV and lupus nephritis is rare.

HIV is associated with a broad spectrum of renal diseases. Of interest is HIV associated immune complex glomerulonephritis with “lupus-like” features. **Objectives:** This study aims to compare and correlate the demographics, epidemiology, pathological and clinical findings of HIV positive patients with lupus nephritis and those with HIV associated immune complex glomerulonephritis with “lupus-like” features. **Methods**: This retrospective chart review study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital in 5 years (2014-2018). We reviewed patients reports that met the criteria for lupus nephritis in HIV and HIV associated immune complex glomerulonephritis with “lupus-like” features and allocated a lupus class according to the report findings. **Results:** Out of 2174 renal reports, 25 (1.14%) patients were diagnosed with lupus nephritis and nine (0.41%) with “lupus-like” HIVICK. There were significant differences in age, serology (urea and creatinine), clinical presentation and lupus class. **Conclusion:** Although co-occurrence of HIV with lupus nephritis and HIV-associated immunecomplex glomerulonephritis with "lupus-like" features is rare, the former is three times more prevalent than the latter.We observed clinical and pathological differences which may be used to diagnose these disease entities.

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Keywords:

Systemic lupus erythematosus and HIV, Lupus nephritis, HIV associated immune complex glomerulonephritis with “lupus-like” features.

ABBREVIATIONS:

ART:	Antiretroviral therapy
AIDS:	Acquired immunodeficiency syndrome
ANA:	Antinuclear Antibodies
Anti-dsDNA:	Anti-double stranded Deoxyribonucleic Acid
CHBAH:	Chris Hani Baragwanath Academic Hospital
CKD:	Chronic Kidney Disease
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
ESRD:	End-Stage Renal Disease
FSGS:	Focal Segmental Glomerulosclerosis
HIV:	Human Immunodeficiency Virus
HIVAN:	Human Immunodeficiency Virus associated Nephropathy
HIVICK:	Human Immunodeficiency Virus associated Immune Complex Kidney
LE:	Lupus erythematosus
NHLS:	National Health Laboratory Service
PCR:	Polymerase chain reaction
SA:	South Africa
SD:	Standard deviation
SLE:	Systemic Lupus Erythematosus
TB :	Tuberculosis

CHAPTER ONE – EXTENDED LITERATURE REVIEW

Human immunodeficiency virus (HIV):

UNAIDS data published in 2019 showed that in 2018 South Africa had the highest rate of HIV infection in the world.7.7 Million people in South Africa are living with HIV. The HIV prevalence rate in the adult population aged between 15 and 49 years is 20.4%. In a study done in 2012 by M. Mabaso et al., HIV prevalence in South Africa through gender and racial lenses showed that HIV infection rates are highest in the black population(1).

Renal diseases in the setting of HIV infection:

Kidney disease is one of the significant complications of HIV infection, and it contributes to mortality and morbidity in both developed and underdeveloped countries. Up to 30% of the population living with HIV present with HIV and AIDS-related kidney diseases, resulting in end-stage renal disease(2).Despite Africa having the highest rate of HIV infection, there is limited available data on the coexistence of HIV and lupus nephritis and HIV associated renal diseases.

HIV associated nephropathy (HIVAN) is the most common classic presentation of kidney disease in HIV, and it presents in young African adults with advanced HIV disease. The APOL1 high-risk allele found in African patients puts them at high risk of HIVAN(3)(4). The second most common kidney disease diagnosed on renal biopsies of HIV positive patients with chronic kidney disease is HIV associated immune complex kidney disease (HIVICK). A less common form of immune complex glomerulonephritis described in HIV infected patients is immune complex glomerulonephritis with “lupus-like” features, which is characterised by histological and structural features resembling lupus nephritis occurring in patients without SLE. There is “full-house” immune staining on immunofluorescence microscopy demonstrating granular glomerular staining for IgG, IgA, IgM, C3 and C1q, with ≥ 1+ intensity (0 to 4+ scale) staining for C1q. (5–10). A single centre study done by

Haas et al. on immune complex glomerulonephritis with “lupus-like” features found that most patients with this disease have poor renal outcomes. This study reviewed 77 renal biopsies from native HIV positive patients from January 1999 to December 2000. Fourteen cases met the criteria for immune complex glomerulonephritis with “lupus-like features” during this period. Immune complex glomerulonephritis with “lupus-like features” is characterised by the histological features of lupus nephritis in a patient without a clinical diagnosis of SLE. The criteria are based on immunofluorescence microscopy showing granular glomerular staining for IgG, IgA, IgM, C3 and C1q, with ≥1+ (0 to 4+scale) staining for C1q and serum negativity for antinuclear antibodies (ANA), or weakly positive (titre ≤1:80) for ANA and negative for anti-double stranded DNA (anti-dsDNA).In the study results, only one patient was an African American. All the patients had microscopic haematuria, and 10 out of 14 had nephrotic syndrome. On light microscopy examination, seven biopsies showed diffuse proliferative glomerulonephritis, six biopsies showed focal proliferative glomerulonephritis, and one case had membranous nephropathy. All but two biopsies showed moderate or severe chronic change, and three showed concurrent HIVAN. Ten of the fourteen patients had end-stage renal disease within one year of renal biopsy. Nine of these ten patients presented with proteinuria >5.0 g/24 hours and nephrotic syndrome, and three of four patients who did not develop ESRD had protein-uria ≤3.0 g/24 hours (11). Patients with HIV have a high prevalence of antinuclear antibodies (ANA) with a low titre, but titres of double-stranded DNA antibodies are unusual (12,13).

The most common glomerular disease in HIV-positive patients was focal segmental glomerulosclerosis with glomerular basement membrane collapse in the pre-ART era. Other kidney diseases include focal segmental glomerulosclerosis with glomerular basement membrane collapse, non-collapsing focal segmental glomerulosclerosis (FSGS), comorbid

chronic kidney disease (CKD), treatment-related kidney injury due to ART therapy and opportunistic infections(14–16).

At a Controversies Conference for Kidney Disease in the Setting of HIV infection, Swanepoel et al. came up with an approach to classify renal disease in HIV infected patients. This classification is based on the affected major tissue compartment, and it is detailed as follows:(15).

Glomerular dominant diseases**:**

The dominant glomerular disorders in this category are podocytopathies and immune complex-mediated glomerulonephritis. **Podocytopathies** manifest as proteinuria and substantial effacement of the podocyte foot processes. Immune complex deposition may be minimal or absent(15). Podocytopathies are divided into four subtypes, classic HIVAN, focal segmental glomerulosclerosis not otherwise specified (FSGS NOS), diffuse mesangial hypercellularity and minimal change disease. The diagnostic features of **classic HIVAN** are collapsing focal segmental glomerulosclerosis without an increase in the mesangial matrix, hyperplasia of visceral epithelium, microcystic dilatation of the renal tubules and interstitial inflammation with oedema(15,16). Tubulointerstitial disease is a significant component of HIVAN, and it appears to be out of phase with glomerular changes (9,15).

FSGS (NOS) in an HIV setting is a diagnosis of exclusion seen in individuals treated with antiretroviral therapy, arterionephrosclerosis of ageing, hypertension, and APOL1 associated nephropathy, which may coexist with HIV. The characteristic features of FSGS NOS in any setting are tubulointerstitial disease and severe podocyte effacement (15).

Diffuse mesangial hypercellularity and minimal change disease are commonly seen in children born with HIV. They show less severe foot process effacement than classic HIVAN and no tubular microcysts or interstitial inflammation (15). Several subtypes of immune

complex diseases have been described with different patterns of immune complex deposition. One of the most typical subtypes is HIV-associated immune complex glomerulonephritis with "lupus-like" features (9,15). Other disorders include IgA nephropathy. Swanepoel et al. found that the occurrence of IgA nephropathy in HIV positive patients was related to IgA deposition directed at the viral antigen or galactose-deficient IgA1, and it manifests with end-stage renal disease. South African studies on IgA nephropathy report unusual electron microscopy findings of subepithelial deposits resembling a "ball in a cup" lesion(9,11). Coinfections in HIV positive individuals are common, and it is essential to rule them out. Coinfection with hepatitis B, hepatitis C and syphilis can cause immune complex diseases like **membranous nephropathy**. **Membranoproliferative pattern glomerulonephritis** is also seen with hepatitis C coinfection (15).

Tubulointerstitial dominant disease in HIV positive patients:

Tubulointerstitial disease is a significant component of classic HIVAN. There are various causative factors for tubulointerstitial disease in HIV positive individuals, and these include antiretroviral drugs such as tenofovir disoproxil fumarate, which causes proximal tubulopathy. NSAIDs, antibiotics, other drugs and tuberculosis infections can cause tubulointerstitial nephritis, which is also seen with TB infection(15). Two rare and readily distinguishable tubulointerstitial injury lesions are related to immunologic dysfunction in HIV positive individuals, (17). The most common of the rare lesions are diffuse infiltrative lymphocytosis syndrome (DLIS) which is an exaggerated immune reaction against HIV infection, and it manifests with CD8+ lymphocytosis and infiltration of the kidneys and other organs(15,17). The other is Immune Reconstitution Syndrome (IRIS) which rarely affects the kidneys(15).

Vascular dominant lesions in HIV:

Before introducing highly active antiretroviral therapy during the HIV/AIDS epidemic, thrombotic microangiopathy was readily seen. Other vascular dominant lesions in HIV may be related to comorbidities such as hypertension and diabetes mellitus. Age-related nephrosclerosis seen in healthy adults is also seen in HIV positive individuals (15).

Systemic Lupus Erythematosus (SLE):

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disease involving multiple organs such as the kidneys, skin, joints, lungs, heart and central nervous system. 50% of patients with SLE present with lupus nephritis (LN), which is characterised by the formation of autoantibodies directed at the cell nucleus, referred to as antinuclear antibodies (ANA) (13-20). The exact aetiology is unknown. However, genetics play a role in SLE development (18). SLE affects women more than men. The female to male ratio is 8:1 to 15:1, and it affects mostly black women of childbearing age. Prepubertal children are also affected, with a prevalence ratio of 4:3. Prognostic factors concerning racial disparities are mostly affected by socioeconomic status, education, and socio-cultural levels. Hispanics and African Americans have a worse prognosis with worse responses to treatment(18). There are also demographic variations in the prevalence and frequency of lupus nephritis(19,20). A study done in Germany in 2002 showed that the prevalence of SLE was 36.7/100 000, with a 4:1 ratio of women to men. The symptoms begin in puberty. There was a significant increase in survival rate (1955 vs 2003: 5-year survival rate 5% vs 95%; 10-year survival rate 0% vs 92%) attributed to early diagnosis and treatment(20,21). Lupus nephritis is an independent predictor of mortality in patients with SLE (37). Black people with SLE are at high risk of developing lupus nephritis (17,37). In a study done in Western Cape Province in South Africa by Brijlal et al., they analysed renal biopsies in patients with SLE from the Renal Unit at Tygerberg Hospital over three decades between January 1983 and December 2012. Out of 427 cases, 315 cases met the criteria for the American College of

Rheumatology criteria for SLE with age above 18 years and no comorbidities. All 315 patients had lupus nephritis, with 90% reported in females. The most common lupus nephritis class was class IV diffuse Lupus Nephritis reported throughout the three decades. The overall five-year survival for patients with class IV lupus nephritis was 67% (95% confidence interval (CI), 60–72%)(23).

SLE and HIV:

The coexistence of SLE and HIV is a rare phenomenon. However, there is limited emerging data on this rare but significant coexistence. In 1988, Kopelman and Zolla-Pazner reported the first case of SLE with HIV infection. Since then, there have been several single case reports or small case series of patients with concomitant SLE and HIV. In literature reviews, 25 cases were reported by Daikh and Holyst in 2001, 30 by Palacios et al. in 2002, 43 by Gindea et al. in 2010, and 57 by Carugati et al. in 2013(21,24).

In the Carugati et al. study dating from 1981 to 2012, 55 patients with SLE and HIV were reported (21). 57 % of cases were recorded in the pre-ART era. 54% of the patients were HIV positive before the diagnosis of SLE, and only seven patients had SLE diagnosis after the initiation of ART. In two patients, the diagnoses of SLE and HIV were made at the same time (21). Out of 55 patients, renal disorders were more commonly described in the paediatric population (85.7 % vs. 51.3%; p=0.05). Twenty-three patients had a renal biopsy performed, and - 21 (91.3%) patients had lupus nephritis. The coexistence of SLE and HIV poses a significant challenge to the diagnosis because of overlapping features and management due to conflicting approaches to disease control (14,25–28). SLE can occur despite the loss of immune competence caused by HIV infection. There are proposed theories on the aetiology of SLE. One suggested that retroviral infections, including HIV, could cause autoimmune diseases like SLE and Sjogren's syndrome due to antibodies to

retroviral proteins or viable and dead organisms (29). The state of immunodeficiency caused by HIV is also responsible for immune dysregulation that facilitates the development of autoimmune diseases. The clinical presentation of HIV is similar to SLE as they both can present with polyarthralgia, oral ulcers, photosensitivity rash, lymphadenopathy, fever, neurological, renal and haematological dysfunctions such as pancytopenia (24,28–30). Opportunistic infections like candidiasis commonly seen in HIV positive patients are also reported in patients with SLE (29).

The symptoms of autoimmunity in HIV positive patients may present as immune reconstitution syndrome (IRIS) with continued immune dysregulation after recovery of CD4+ T cells with ART initiation (29). The management of SLE and HIV is contradictory. Immunosuppressants manage SLE, whereas immune boosters manage HIV. HIV-related immunosuppression improves lupus erythematosus symptoms, and the initiation of ART with subsequent improvement in CD4+ T cells may trigger lupus flares (29)(31)(32). CD4+ T lymphocytes have an essential role in the pathogenesis of SLE. It has been found that during the period of immunosuppression before initiation of ART, the symptoms of SLE generally improve. The presence of immunosuppression in the setting of HIV and SLE also predispose to opportunistic infections posing a significant challenge in the management of both diseases (32).

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CHAPTER TWO – SUBMISSIBLE FORMAT

COMPARISION BETWEEN LUPUS NEPHRITIS IN HIV POSITIVE PATIENTS AND HIV-ASSOCIATED IMMUNE COMPLEX GLOMERULONEPHRITIS WITH "LUPUS-LIKE" FEATURES: a clinico-pathologic study

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease seen commonly in black females of childbearing age. More than half of the patients present with renal disease or lupus nephritis complications. Coinfection with HIV in patients with lupus nephritis is rare. Despite Africa having the highest rate of HIV infection in the world, and there is no available data on the coexistence of HIV and Lupus nephritis. HIV is associated with a wide spectrum of renal diseases, including "lupus-like" HIV-Associated Immune Complex Kidney Disease (HIVICK). The most prevalent renal lesions in "lupus-like" HIVICK is diffuse proliferative lupus nephritis **Objectives:** This study aimed to compare and correlate the demographics, epidemiology, pathological and clinical findings of HIV positive patients with lupus nephritis and those with "lupus-like" HIVICK. **Methods**: This retrospective chart review study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital in 5 years (2014-2018). We reviewed case reports that met our criteria for cases with lupus nephritis and cases with "lupus-like" HIVICK and allocated a lupus class according to the report findings. **Results:** Out of 2174 renal reports, 25(1.14%) patients were diagnosed with lupus nephritis and nine (0.41%) with "lupus-like" HIVICK. There were significant differences in age, serology (urea and creatinine), clinical presentation and lupus class. **Conclusion:** The occurrence of both HIV associated lupus nephritis and 'lupus like' HIVICK is rare. In our setting, the former is more common than the latter. We observed clinical and pathological differences which may be used to diagnose these disease entities.

KEYWORDS: SLE, Lupus nephritis, HIVICK, HIV, South Africa

INTRODUCTION

The coexistence of HIV and SLE is an infrequent life-threatening condition with few reported cases worldwide (25,31,32,34). SLE is a complex, autoimmune disease that affects multiple organs. It is characterised by loss of self-antigen tolerance and the formation of autoantibodies directed against the DNA and other components of the cell nucleus, termed antinuclear antibodies (ANA). The exact aetiology is unknown, but evidence supports that genetics play a major role with a heritable chance (33). The majority of the available data are case reports, and there is limited data on studies done in Africa. The prevalence of SLE in HIV positive patients in South Africa is not known. The prevalence of SLE in the U.S. is estimated between 0.05% and 0.1% of the population; The disease disproportionately affects African Americans (prevalence estimates:0.009%, white men; 0.066%, white women; 0.038%, African-American men; and 0.282%, African-American women) (34).

There are reports on cases of HIV associated nephropathy with “lupus-like features”, which is characterised by histological, immunohistologic and ultrastructural features of lupus nephritis occurring in a patient without SLE (35).

Forty-two million people worldwide are living with HIV. Almost 30 million people who are HIV positive live in Africa (36)(37). In 2018, rate of HIV infection in the world, with 7.7 million people living with HIV. The HIV prevalence rate in the adult population aged between 15 and 49 is 20.4%, and the infection rates are highest amongst the black population (1). There is limited data published on lupus nephritis in the HIV setting. Thirteen patients were reported to have SLE and HIV in a South African case series study by Mody et al. All the patients were females, eleven African blacks and two Indians. They noted a reduction in SLE disease activity in these patients (24).

This study aimed to compare the demographic, pathological and clinical findings of HIV positive patients with lupus nephritis and those with immune complex glomerulonephritis with “lupus-like” features.

METHODS

Ethical considerations:

Ethical clearance was granted by the Human Research Ethics Committee of the University of The Witwatersrand (Ref: M200716).

Sample collection:

This study was a retrospective chart review from a single laboratory, where cases are received from 4 tertiary hospitals conducted at Charlotte Maxeke Johannesburg Academic Hospital at the National Health Laboratory Services (NHLS) Department of Anatomical Pathology, University of the Witwatersrand.

We included and reviewed all cases of biopsy-proven lupus nephritis in HIV positive patients and patients with "lupus-like" HIVICK diagnosed from 1 January 2014 to 31 December 2018. Biopsies from HIV positive patients clinically suspected to have lupus nephritis but where there was inadequate material on biopsy for accurate histologic diagnosis, biopsy reports with inadequate, incomplete or unclear information including unknown HIV status, and post-transplant biopsies were excluded.

Biopsy reports were retrieved from the NHLS database using the current TrakCare laboratory information system with SNOMED codes T-71000 for kidney and M-40000 for inflammation. All kidney biopsies received at the hospital are given a laboratory number and a unique renal biopsy number. These details are entered in a separate logbook in the laboratory. The logbook was also accessed to retrieve cases that meet the criteria for inclusion in this study. Data were extracted from the pathology reports and the NHLS database (routinely collected laboratory results).

Statistical Analysis

Data analyses were performed on STATA® 16. Normality distribution of quantitative variables was performed using the Shapiro-Wilk W test. P-value P-values of > 0.05 were considered normally distributed, while P-values of <0.05 were considered not normally distributed. Normally distributed variables were summarised as mean ±SD, and non-normally distributed variables were summarised as median ± IQR. All qualitative variables were summarised as percentages. Differences between HIV + lupus nephritis group and the "lupus-like" HIVICK group were determined by t-test or fisher's exact/ chi-square, as appropriate. A p-value of ≤ 0.05 was considered significant.

RESULTS

Demographics

Demographics of HIV positive patients with lupus nephritis:

Two thousand one hundred seventy-four renal biopsies were received during the study period at the NHLS/Charlotte Maxeke Johannesburg Academic Hospital. The demographic details are in table 1. Twenty-five (1.14%) patients were HIV positive with lupus nephritis. The age ranged from 13 to 59 years with a mean age of 37 ± 9.36 years (Table 1). There were 23 (92%) females (n= 25) and two (8%) males. Twelve (48%) patients were from Chris Hani Baragwanath Academic Hospital. Seven (28%) patients were from Charlotte Maxeke Johannesburg academic hospital, and six (24%) patients were from Helen joseph hospital (Table 1).

Demographics of patients with HIV associated immune complex glomerulonephritis with "lupus-like" features:

Nine (0.41%) patients with "lupus-like" HIVICK were identified. Their ages ranged from 19 to 41 years with a mean age of 30 ± 7.72 years. Seven (77%) patients were female, and two (22.2%) were males. Four (44%) patients were from Chris Hani Baragwanath, three (33%) were from Helen Joseph hospital. Charlotte Maxeke Johannesburg academic hospital and Polokwane hospital had one (11.1%) patient.

Clinical presentation

Clinical presentation of HIV positive patients with lupus nephritis:

The clinical presentation of SLE was documented in nine (36 %) (n=25) patients (Figure 1). Nephrotic syndrome was documented in seven (28%) patients. There were seven (28%) patients with chronic renal failure. A combined nephrotic/nephritic syndrome was seen in two (8%) patients. Nephritic syndrome, hypertension, deep venous thrombosis and anaemia

were reported in one (4%) patient. None of the patients had isolated haematuria, acute renal failure or tuberculosis infection (Figure 1).

Clinical presentation in patients with HIV associated immune complex glomerulonephritis in "lupus-like" features:

There were seven (77%) patients with nephrotic syndrome (Figure 1). Chronic renal failure was seen in four (44.4%) patients and acute renal failure in three (33. 3%). Haematuria was documented in two (22%) patients. One (11.1%) patient presented with nephritic syndrome. Three (33.3%) patients had hypertension, and two (22.2%) had tuberculosis (Figure 1).

Serological findings

Serological findings in HIV positive patients with lupus nephritis:

ANA was positive in 20 (80%) (n=25) patients (Table 1). A negative ANA was recorded in two (8%) patients, and in three (12%) patients, the ANA status was not documented. Nine (36%) patients with a positive ANA demonstrated a speckled staining pattern. A homogenous staining pattern was reported in four(16%) patients. The staining pattern was not documented in ten (40%) patients. The highest ANA titre of 1280IU/mL was documented in three patients (Table 1). The anti-double stranded DNA was positive in five (20%) patients, three had an anti-ds-DNA of 160IU/mL, and two were 40IU/mL. A negative anti-ds-DNA was recorded in 11 (44 %) patients. The double-stranded DNA was not stated in nine (36%) patients.

C3 and C4 values were recorded in 11 (44%) and the median values were 0.53 ± 0.99 g/L and 0.15 ± 0.18 g/L, respectively (Table 1).

The urine albumin creatinine ratio was documented in 16 (72%) patients. There was heavy proteinuria in 7 (28%) patients. The mean protein creatinine ratio was 0.47± 0.22 g/mmol.

The urea and creatinine were recorded in 24 (96%) patients with mean values of 8.3875 mmol/L and 126.4583 umol/L, respectively.

The CD4 count was recorded in 20 (80%) patients with the median value of 349.5 ± 266.5 cells/uL. The viral load was recorded in 15 (60%) patients. The mean viral load was 291 copies/mL with a standard deviation of 653.4873. The viral load was undetectable in 9 (36%) patients (Table 1).

Serology studies in patients with HIV associated immune complex glomerulonephritis in "lupus-like" features:

ANA was negative in eight out of the nine (88.8%) patients. No results were recorded in one patient. The anti-ds-DNA was negative in all cases. C3 and C4 values were recorded in 4(44.4%), and they ranged from 0.5 to 1.54g/L and 0.06 to 0.43g/L. The urea and creatinine were documented in all the patients, and they ranged was from 4.4 to 27.6mmol/L and 62 to 573mmol/L, respectively. Urine albumin and creatinine ratio was documented in 7(77.7%) and ranged from 0.109 to 1.7g/g. The CD4 count was documented in 7(77.7%) patients, and it ranged from 94 to 851cells/uL. The viral load was documented in five (55.5%) patients. The lowest viral load was less than the detectable limit, and the highest viral load was 8610 copies/mL.

Histological Findings: Lupus class correlation with viral load (see Table 2) and CD4 count (see Table 3):

Renal biopsy lupus class correlation with viral load and CD4 count in HIV positive patients with lupus nephritis:

All six lupus classes were found in this cohort (Figure 2). One (4%) patient had lupus class I and the CD4 count was 349 cells/uL with a viral load less than the detectable limit. Two patients had class II lupus nephritis with a CD4 count of 450 cells/uL in one patient and undocumented in the other (Table 3). The viral load was less than the detectable limit in one

patient, and no documentation of viral load in the other patient (Table 2). Five (20%) patients had class III lupus nephritis, and the CD4 count was documented in four patients, ranging from 134 to 350cells/uL. The viral load was less than the detectable limit in four patients. Two (8%) patients had class IV lupus nephritis with viral loads of less than the detectable limit and 144 copies/mL, respectively (Table 2). The CD4 count was not documented in both patients. Four (16%) patients had class V lupus nephritis and their CD4 counts ranged from 29 to 834 cells/uL. The viral load was documented in two patients with 135 and 1070 copies/mL respectively. Six (24%) patients had class III + V lupus nephritis with the CD4 count ranging from 337 to 1300. The viral load was less than the detectable limit in one patient, 1360 in the other and undocumented in four patients. One (4%) patient had class IV + V lupus nephritis, and the CD4 count and viral load were not documented.

Five (20%) patients had class III focal lupus nephritis. Four of these patients had a viral load less than the detectable limit, and the CD4 count ranged from 134 to 350 cells/mL. One patient's viral load was not documented.

There were four patients (16 %) with class V membranous lupus nephritis (Figure 2). All four patients had documented CD4 counts ranging from 29 to 834 cells/mL (Table 3). The viral load was documented in two patients with 135 and 1070 copies/mL values. The other two patients' viral loads were not documented (Table 2).

Three patients (12 %) had class II mesangial proliferative lupus nephritis. In these patients, one patient had a viral load of less than the detectable limit with a CD4 count of 272cells/uL, and the second patient had a viral load of 2413 copies/ mL with an undocumented CD4 count. The third patient had a CD4 count of 450 cells/uL with an undocumented viral load.

Two (8%) patients had class IV diffuse lupus nephritis (Figure 2). One of these patients had a viral load less than the detectable limit and the other 144 copies/mL (Table 2). The CD4 count was not documented in both patients (Table 3).

Two patients had combined lupus class VI + V (Figure 2). The CD4 counts were 98 and 476 cells/uL, respectively. The viral load was 129 copies/mL, and the other patient's viral load was not documented.

Only one patient (4%) had a combined lupus nephritis class V + VI. This patient had a viral load of less than the detectable limit and a CD4 count of 443 cells/uL. There were two (8%) patients with class VI + V lupus nephritis, and the CD4 count was 98 and 476 cells/uL. The viral load was documented in one patient, and it was 129copies/mL

Renal biopsy lupus class correlation with CD4 count and viral load in patients with HIV associated immune complex glomerulonephritis in "lupus-like" features:

Four lupus classes were found in this cohort (Figure 2). Class II lupus nephritis was recorded in one (11.1%) patient, and the CD4 count was 851cells/uL (Table 3), and the viral load was less than the detectable limit (Table 2). One (11.1%) patient had class III lupus nephritis, the CD4 count was 703cells/uL, and the viral load was not stated. Five (55.5%) patients had class IV lupus nephritis. The CD4 count ranged from 94 to 661cells/uL in four patients with documented values. The viral load ranged from less than the detectable limit to 8610copies/mL in three patients with documented values. Two (22.2%) patients had class V lupus nephritis with a CD4 count of 568cells/uL and a viral load of less than the detectable limit documented in one patient (Table 2). The other patient's viral load and CD4 count were not documented (Table 3).

The presence of tubulointerstitial changes:

Tubulointerstitial changes in HIV positive patients with lupus nephritis:

Tubulointerstitial changes were seen in 23 (92%) n= 25 patients (Table 1). There was acute tubular necrosis in 12 (48%) patients. Chronic interstitial nephritis was seen in 20 (80%) patients (Table 1).

Tubulointerstitial changes in patients with HIV associated immune complex glomerulonephritis with "lupus-like" features:

All nine patients had tubulointerstitial changes (Table 1).

DISCUSSION

This retrospective study included data from 1 January 2014 to 31 December 2018 of all patients who are HIV positive with biopsy-proven lupus nephritis and patients with HIV associated immune complex glomerulonephritis with “lupus-like” features that were seen at the NHLS/ Charlotte Maxeke Johannesburg Academic Hospital. The number of patients with lupus nephritis and concurrent HIV infection was 25 (1.14and there were nine patients (0.14%) with "lupus-like" HIVICK. The majority of the patients in both groups were women of childbearing age. HIV positive patients with lupus nephritis were older than those with “lupus-like” HIVICK with the mean age of 37,24 ± 9,364 and 30,11 ±7,721 respectively. Many patients were from Chris Hani Baragwanath hospital with 48% and 44% cases in HIV positive with lupus nephritis and “lupus-like HIVICK”, respectively. Chris Hani Baragwanath is the largest hospital in Africa, 90% of the patients served there are black African. Twenty-five cases of lupus nephritis with concurrent HIV infection is the highest number ever recorded in the literature from a single centre focusing specifically on lupus nephritis and HIV rather than just SLE and HIV. In the literature review by Carugati et al. from 1988-2012, they reported 55 patients with SLE and HIV and only 21 patients were diagnosed with lupus nephritis.

In our five year study period,we found nine patients with “lupus-like” HIVICK Among the published studies, the highest number of cases with lupus-like HIVCK is 14, recorded by Haas et al. over five years.

Both cohorts' most common clinical presentation was nephrotic syndrome and chronic renal failure. Two (22%) patients with “lupus-like” HIVICK had an opportunist infection of TB at presentation. None of the patients with lupus nephritis had any opportunistic infections. ANA was positive in 80%, and 36% demonstrated a speckled pattern, while 24% had a

homogenous staining pattern. The ANA ranged from 160 to 1280IU/mL. The anti-dsDNA was positive in 20% of patients with lupus nephritis. Although the literature states that HIV infection may be associated with a positive ANA with a low titre, none of our patients with "lupus-like" HIVICK had a positive ANA, and as expected, there was no positive anti-dsDNA in this cohort.

In patients with lupus nephritis, eight (32%) patients had low C3 values and five (20%) had a low C4 values. Only one patient in the lupus-like HIVICK cohort had low C3 and C4 values, suggesting an immune complex disease is not active in this cohort.

Patients with "lupus-like" HIVICK showed the worst renal dysfunction as demonstrated by the renal function tests. There was heavy proteinuria in 7(28%) {n=25} patients with lupus nephritis and 5(55.5%) {n=9} patients with "lupus-like" HIVICK. The urea and creatinine levels were deranged in 10(40%) patients with lupus nephritis and 7(77%) patients with "lupus-like" HIVICK. The CD4 count and viral load showed marked variation in both cohorts and correlation with the lupus class category. The viral load was undetectable in 9 (36%) and 3 (33%) patients with lupus nephritis and with "lupus-like" HIVICK, respectively. A normal CD4 count was recorded in 10(40%) and 5(55.5%) patients with lupus nephritis and "lupus-like HIVICK, respectively.

The most common lupus class category in patients with lupus nephritis was class III + V lupus nephritis with 6(24%) patients, followed by class III lupus nephritis with five (20%). Class IV lupus was the most prevalent in patients with "lupus-like" HIVICK with 5(55%) patients. These findings are similar to a study done by Haas et al. on cases with "lupus-like" HIVICK, where he reported that 50% of the patients had diffuse proliferative lupus nephritis. We found that combined lupus class categories were only reported in patients with lupus nephritis.

We found two male patients in each cohort. In the lupus nephritis group, one had class II lupus nephritis, and the other had class VI + V lupus nephritis. In the "lupus-like" HIVICK, one male patient had IV lupus nephritis, and the other had class V lupus nephritis. Our study showed variation in viral load and CD4 count values seen in each lupus class and no gender preference in the lupus class category.

Our study shows that patients with "lupus-like HIVICK have worse renal outcomes than those who are HIV positive with lupus nephritis. The difference in renal outcomes could be due to surveillance of renal function in patients with SLE and HIV, which leads to early detection of the disease. Renal biopsies performed in patients with "lupus-like HIVICK were done due to the clinical presentation of renal failure. Therefore the renal disease stage was more advanced than patients on surveillance.

LIMITATIONS

The limitation in this study is the consistency in the documentation of patient blood results data. Many patients had undocumented viral load and CD4 count, which limited our ability to correlate lupus classes with these variables.

CONCLUSION

This study aimed to compare the demographic, pathological and clinical findings of HIV positive patients with lupus nephritis and those with "lupus-like" HIVICK. According to the English literature, we found three times more HIV positive patients with lupus nephritis than those with 'lupus like' HIVICK, which is the highest number reported from a single laboratory. Both groups were composed predominantly of females of childbearing age and presented clinically with nephrotic syndrome and chronic renal failure. There was no clear correlation between lupus class, gender, viral load and CD4 count.. However, lupus class

prevalence differed in the two groups, with the most prevalent lupus class in the HIV positive lupus nephritis group being class III + V. In contrast, the most prevalent lupus class in the "lupus-like" HIVICK group was class IV lupus nephritis. Class IV lupus nephritis as the commonest lupus class in the "lupus-like" HIVICK cohort is a significant finding similar to what has been reported in the literature, and it is associated with poor renal outcomes.

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TABLES AND FIGURES

Table 1: Characteristics of patients who are HIV positive with lupus nephritis and lupus-like HIVICK

Variables	**HIV + lupus nephritis**	**"lupus-like" HIVICK**	**p-value**
Demographic data			
n (%, TOTAL 2174)	25 (1.14%)	9 (0.41%)	**0.0029**
Age (mean ± SD)	37,24 ± 9,364	30,11 ±7,721	**0,0388**
Gender (F:M)	23:2	7:2	0,3512
Referral hospital			N/A
CMJAH	7	1	
HJH	6	3	
CHBAH	12	4	
Polokwane		1	
Clinical data			
SLE specific variables			
ANA	Positive 20/25 (80%)	Negative 8/9 (88.9%)	
ANA pattern: Homogenous Speckled N/A NS	 4 (16%) 9 (36%) 2 (8%) 10(40%)		

Anti-ds-DNA (median± IQR)	Positive 5/16 (31.25%) 40,0000±120,0000	NS	
C3 (median± IQR)	0,5300± 0.99	1,05± 0.61	0,2149
C4 (median± IQR)	0.15± 0.18	0,32± 0.245	0,1499
Urea (median± IQR)	6.15±5.25	14.3 ± 9.6	**0,0236**
Creatinine (median; IQR)	77.5 ± 52.0	214 ± 115	**0,0109**
Urine albumin: Creatinine ratio (mean ± SD)	0,4731 ± 0,2196	0,7707 ± 0,6174	0,2608
HIV monitoring variables			
CD4 count (median, IQR)	349.5±266.5	568 ± 534	0,4718
Viral load (Median, IQR)	0± 144	0 ± 238	0,8055
Pathology			
Tubulointerstitial changes present	23 (92%)	9 (100%)	
Acute tubular & Chronic interstitial nephritis	12 (48%)	N/A	

Chronic interstitial nephritis	20 (80%)	N/A	

Table 2: Lupus nephritis class correlation with viral load.

Lupus class	**Number of HIV + lupus nephritis N (%)**	**Mean +/-SD Viral load HIV + LN**	**"lupus like" HIVICK N (%)**	**Mean +/-SD Viral load "lupus like" HIVICK**
I (nr; %)	1 (4%)	0	- -	-
II	2 (8%)	1206,5±1706,25	1 (11,1%)	0
III	4 (16%)	0	1 (11%)	0
IV	2 (8%)	72 ± 101,8	5 (55%)	2949,3 ± 4903,7
V	2 (8%)	602,5 ± 661,1	2 (22,2%)	0
VI	-	-	-	-
III + V	2 (8%)	680 ± 961.7	-	-
IV + V	-	-	-	-
V+VI	1 (4%)	0	-	-
VI + V	1 (4%)	129	-	-

Table 3: Lupus nephritis class correlation with CD4 count.

Lupus class	**Number of HIV + lupus nephritis N (%)**	**Mean +/-SD CD4 in HIV + LN**	**"lupus-like" HIVICK N (%)**	**Mean +/-SD CD4 count in "lupus-like" HIVICK**
I	1 (4%)	349	-	-
II	3 (12%)	361 ± 125,9	1 (11,1%)	851
III	5 (20%)	269.5 ± 98,99	1 (11.1%)	703
IV	2 (8%)	-	5 (55.5%)	333 ± 256,4
V	4 (16%)	475.5 ± 365,8	2 (22,2%)	568
VI	0	-	-	-
III + V	6 (24%)	586.8 ± 369,6	-	-
IV + V	2 (8%)	NS	-	-
V+VI	1 (4%)	443	-	-
VI + V	2 (8%)	287 ±267,3	-	-

Figure 1: Clinical presentation.

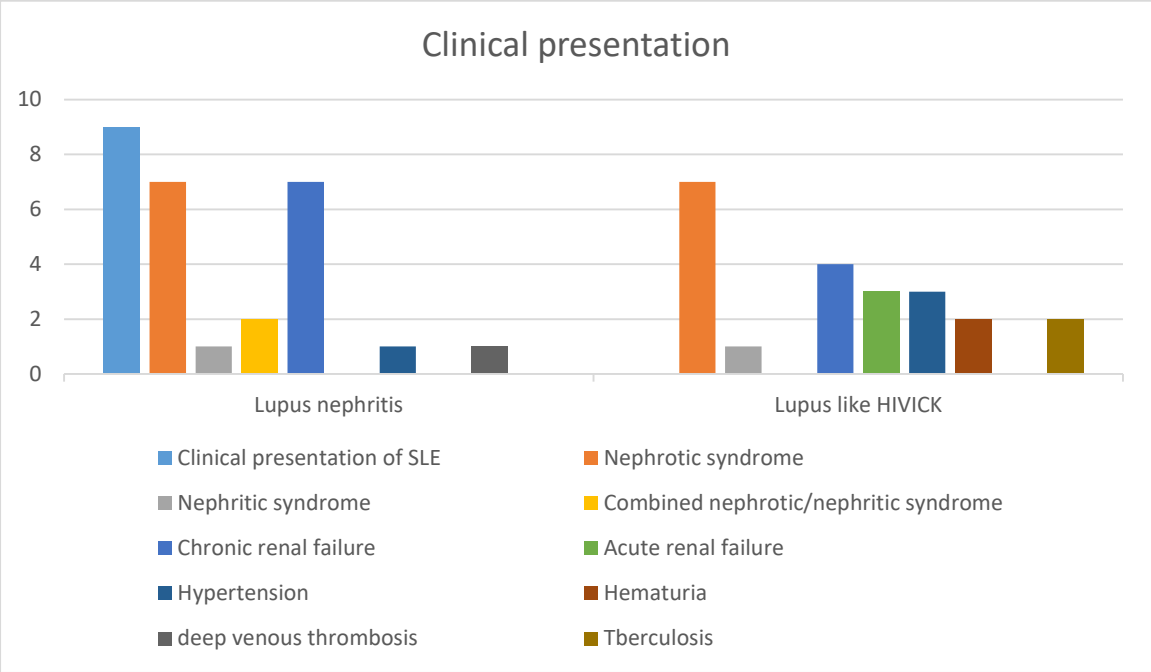
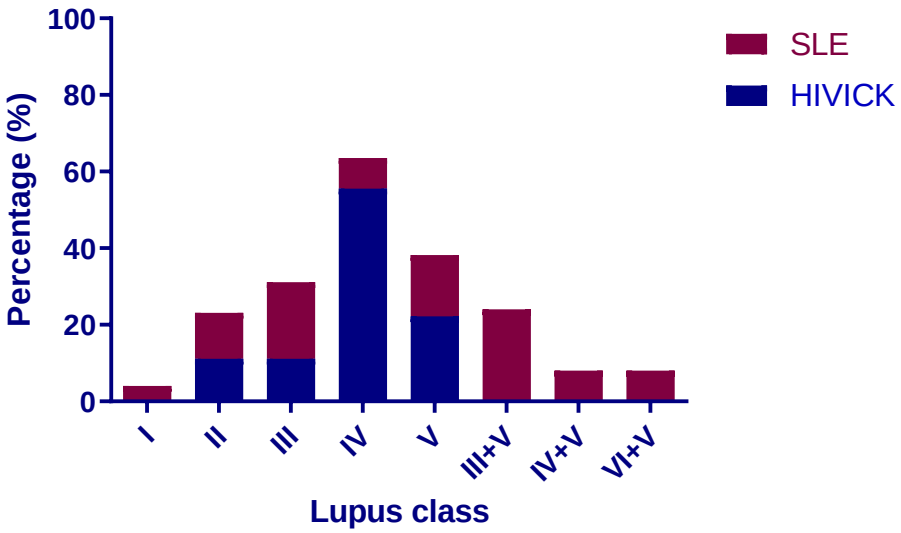


Figure 2: Lupus class prevalence.



CHAPTER THREE – APPENDICES

APPENDIX A – DATA COLLECTION SHEET.

Study number:

Age:

Gender: M/F

Clinical presentation

Nephrotic syndrome:

Nephritic syndrome:

Combined nephrotic and nephritic syndrome:

Isolated haematuria:

Acute renal failure:

Chronic renal failure:

Hypertension:

Other:

ANA serology: Pos, titre/Neg

Anti-double stranded DNA: Pos/Neg

C3 and C4:

Urea:

Creatinine:

Urine albumin: creatinine ratio:

CD4 Count:

Viral load:

Biopsy findings: Lupus class: I/II/III/IV/V/IV, combined III+V/IV+V

Tubulo-interstitial findings:

APPENDIX B: RESEARCH PROTOCOL

COMPARISION BETWEEN LUPUS NEPHRITIS IN HIV IN POSITIVE PATIENTS AND HIV-ASSOCIATED IMMUNE COMPLEX GLOMERULONEPHRITIS WITH "LUPUS-LIKE" FEATURES: A clinico-pathologic study

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Co-supervisor: Pulane Mosiane, MBBCh, FCPath (SA) (National Health Laboratory Service)

Position: Consultant Pathologist

A protocol submitted for the Degree of Master of Medicine in the Division of Anatomical Pathology, School of Pathology, University of the Witwatersrand and National Health Laboratory Service

1

APPENDIX C- ETHICS CERTIFICATE.

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200716

NAME: Dr MM Mathaba
(Principal Investigator)

DEPARTMENT: School of Pathology
Department of Anatomical Pathology
Medical School
University

PROJECT TITLE: Comparison between lupus nephritis in HIV positive and HIV associated immune complex glomerulonephritis with lupus-like features: a clinical-pathologic study

DATE CONSIDERED: 2020/07/31

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr P Ma Dr P Maganagane

APPROVED BY: _____
Dr CB Penn son, HREC (Medical)

DATE OF APPROVAL: 2021/12/21

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly, progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in July and therefore reports and re-certification will be due in the month of July each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

_____ 10 January 2021
Signature of Principal Investigator Date

APPENDIX D: TURN IT IN REPORT.