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Spectrum of Renal Histopathological Findings in HIV-Positive Patients: A Case Series from a Tertiary Care Centre in Northeast India

[1]Manjuri Sharma, Professor, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India

[2]Pritam Kumar, Resident, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India

[3]Prodip Kr Doley, Professor, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India

[4]Gayatri Pegu, Associate Professor, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India

[5]Miranda Pegu, Associate Professor, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India

Corresponding Author: Pritam Kumar, Resident, Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, Assam, India

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Abstract

Aims and Objectives: To describe the diversity of renal histopathological findings in HIV-positive individuals undergoing kidney biopsy, and to emphasize the importance of renal biopsy in distinguishing HIV-related from unrelated causes of renal dysfunction.

Materials and Methods: A retrospective analysis of four HIV-positive patients who underwent kidney biopsy for evaluation of renal dysfunction or proteinuria at our centre was conducted. Clinical details, antiretroviral therapy (ART) status, biochemical parameters, and biopsy findings were reviewed. Biopsies were evaluated using light microscopy (LM) and direct immunofluorescence (DIF); immunohistochemical staining for PLA2R was performed where indicated.

Results: Four distinct histopathological patterns were identified: (A) Membranous glomerulopathy with PLA2R positivity, consistent with primary membranous nephropathy unrelated to HIV; (B) Acute tubular injury with non-proliferative glomerular morphology, likely drug-induced or ischaemic; (C) Non-proliferative glomerular changes with low-intensity trace mesangial immune deposits, suspicious for minimal change disease or early HIVAN, with SLE requiring exclusion; and (D) Diabetic nephropathy (Class III) with nodular glomerulosclerosis in a patient with established diabetes

mellitus and HIV co-infection. This spectrum highlights that renal lesions in HIV-positive individuals are not always directly attributable to HIV infection.

Conclusion: Renal biopsy plays a critical role in accurately diagnosing the underlying cause of kidney disease in HIV-positive patients. Primary glomerular disease, diabetic nephropathy, and drug-induced injury must be considered alongside HIV-associated nephropathy (HIVAN). Tailored management depends on precise histological diagnosis.

Keywords: HIV nephropathy; kidney biopsy; PLA2R; membranous nephropathy; diabetic nephropathy; acute tubular injury; minimal change disease; HIVAN; renal pathology in HIV

Introduction

The advent of highly active antiretroviral therapy (HAART) has dramatically altered the natural history of HIV infection, transforming it from a rapidly fatal illness to a manageable chronic condition. As survival has improved, the spectrum of comorbidities in HIV-positive individuals has broadened considerably, with renal disease emerging as a significant contributor to morbidity and mortality in this population.

HIV-associated nephropathy (HIVAN), classically characterised by collapsing focal segmental glomerulosclerosis, diffuse tubular microcystic dilation, and heavy proteinuria, has historically been regarded as the dominant renal lesion in HIV-infected individuals. However, growing evidence — particularly from regions with high HIV burden — indicates that the renal disease spectrum in HIV-positive patients is far broader and includes immune-mediated glomerulonephritides, drug-induced nephrotoxicity, and comorbidity-related conditions such as diabetic nephropathy and hypertensive nephrosclerosis.

Clinically differentiating these entities on the basis of presentation alone is often unreliable, as proteinuria, haematuria, and elevated serum creatinine can occur across the entire spectrum. Renal biopsy thus remains the gold standard for diagnosis and is essential for guiding specific, histology-directed therapy. Despite this, biopsy is underutilised in HIV-positive patients, partly due to concerns about coagulopathy and partly due to the clinical assumption that renal disease is attributable to HIV itself.

We present a case series of four HIV-positive patients who underwent kidney biopsy at a tertiary nephrology centre in Northeast India, illustrating the heterogeneity of renal histopathological diagnoses encountered in this population and underscoring the indispensability of tissue diagnosis.

Materials and Methods

This is a retrospective descriptive case series of four HIV-positive patients who underwent percutaneous kidney biopsy at the Department of Nephrology, Gauhati Medical College and Hospital, Guwahati, between 2024 and 2025. Biopsy was indicated in each case for evaluation of unexplained renal dysfunction, nephrotic-range or significant proteinuria, or both.

All biopsies were processed at Dr. Lal Path Labs, National Reference Laboratory, New Delhi. Tissue was evaluated by light microscopy using haematoxylin and eosin (H&E), Periodic Acid–Schiff (PAS), Masson's Trichrome (MT), silver methenamine, and Congo red stains. Direct immunofluorescence (DIF) was performed on fresh frozen tissue using antibodies against IgA, IgG (with IgG subclasses), IgM, C3, C1q, kappa and lambda light chains. Immunohistochemistry (IHC) for PLA2R (phospholipase A2 receptor) was performed in cases with suspected membranous nephropathy. Clinical data

including ART status, biochemical parameters, 24-hour urinary protein, and serum creatinine were reviewed from case records.

Patient identities have been anonymised and are referred to as Patient 1 through Patient 4. Informed consent was obtained from all patients for biopsy as part of standard clinical care.

Case Presentations

Case A — Membranous Glomerulopathy with PLA2R Positivity (Primary Membranous Nephropathy)

Clinical Presentation

Patient 1 was a 38-year-old male with a known history of hypertension and HIV infection (reactive), on HAART. He presented with facial puffiness and bilateral pedal oedema. Investigations revealed a serum creatinine of 1.17 mg% and a 24-hour urinary protein of 2.9 g, indicating sub-nephrotic to nephrotic-range proteinuria. Serum cholesterol was within acceptable limits. Urine microscopy was unremarkable.

Biopsy Findings

Light Microscopy: Sections stained with H&E, PAS, MT, silver methenamine, and Congo red included renal medulla and cortical parenchyma containing up to 14 glomeruli, of which 4 (28.5%) were globally sclerosed. The remaining viable glomeruli appeared enlarged and revealed diffuse thickening of capillary walls with membrane texture alterations and intramembranous 'mottling' on silver methenamine staining. Segmental increase in mesangial matrix was noted in a few glomeruli and one exhibited segmental tuft sclerosis. There was no evidence of tuft necrosis, subendothelial or Congophilic deposits, intracapillary thrombi, or crescent formation. Tubular atrophy and interstitial fibrosis involved approximately 10–12% of the sampled cortex. Focal cytoplasmic vacuolar change, patchy acute tubular injury with epithelial simplification and loss of brush borders, and a few hyaline casts in tubular lumina were observed. Arteries showed mild medial thickening and subintimal sclerosis; arterioles revealed hyalinosis lesions.

Direct Immunofluorescence (DIF): Up to 7 glomeruli were sampled. IgG showed 3+ granular capillary wall staining, with IgG1 2+ and IgG4 3+ granular capillary wall positivity (IgG2 and IgG3 negative). IgA and IgM were negative. C3 and C1q showed trace capillary wall granular staining. Kappa and lambda light chains both showed 3+ granular capillary wall staining.

Immunohistochemistry: Staining for PLA2R showed diffuse granular positivity/overexpression along glomerular capillary walls. Staining for NELL-1 was negative.

Impression

Membranous glomerulopathy (MGN), PLA2R positive — consistent with primary (idiopathic) membranous nephropathy, unrelated to HIV infection. The dominant IgG4 subclass, capillary wall granular pattern, and PLA2R positivity confirm an autoimmune podocytopathy.

Clinical Correlation and Management

The diagnosis of primary membranous nephropathy was established. Given the PLA2R positivity, serum anti-PLA2R antibody titres were recommended for disease monitoring. Management was initiated as per standard guidelines for primary MN, with supportive antiproteinuric therapy and consideration of immunosuppression based on risk stratification. HAART was continued.

Case B — Acute Tubular Injury with Non-Proliferative Glomerular Morphology

Clinical Presentation

Patient 2 was an HIV-positive individual [clinical details pending]. Renal biopsy was indicated for evaluation of renal dysfunction in the setting of HIV infection and ongoing medication exposure. [Age, sex, ART status, serum creatinine and 24-hour urinary protein data pending].

Biopsy Findings

[Full biopsy report data pending]. Based on available information, light microscopy revealed non-proliferative glomerular morphology with evidence of acute tubular injury. Immunofluorescence studies did not reveal significant immune complex deposition.

Impression

Acute tubular injury with non-proliferative glomerular morphology — most likely drug-induced (antiretroviral or other nephrotoxic agents) or ischaemic in aetiology. HIVAN was not supported by the morphological features.

Clinical Correlation and Management

[Management details pending]. Review of potentially nephrotoxic medications and optimisation of renal perfusion were advised. HAART regimen was reviewed for nephrotoxic agents such as tenofovir disoproxil fumarate (TDF).

Case C — Non-Proliferative Glomerulopathy with Trace Mesangial Immune Deposits (MCD vs. Early HIVAN; SLE to Exclude)

Clinical Presentation

Patient 3 was a 47-year-old female with a known history of HIV infection, on HAART since 2014. She presented with bilateral lower limb swelling and raised blood pressure. She had been on prednisolone. Investigations revealed a serum creatinine of 0.9 mg% and a 24-hour urinary protein of 0.3 g (on prednisolone), suggesting partial response to corticosteroid therapy. Serum cholesterol was 215 mg/dL. Urine RBC was nil.

Biopsy Findings

Light Microscopy: Sections stained with H&E, PAS, MT, silver methenamine, and Congo red sampled a small renal cortical parenchymal area containing up to 9 glomeruli, none globally sclerosed. The glomeruli revealed focal dilatation and congestion of capillary lumina with non-proliferative morphology. Occasional glomeruli showed mild increase in mesangial matrix. Peripheral capillaries did not appear thickened. There was no evidence of segmental sclerosis, tuft necrosis, subendothelial or Congophilic deposits, or crescent formation. Tubular atrophy and interstitial fibrosis involved less than 10% of sampled cortex. Focally prominent cytoplasmic vacuolar change and focal minimal chronic interstitial inflammation were observed. Small arteries appeared unremarkable; arterioles revealed vacuolisation in smooth muscle cells of the media.

Direct Immunofluorescence (DIF): Up to 3 glomeruli were sampled. All parameters — IgA, IgG (IgG1, IgG2, IgG3, IgG4), IgM, C3, C1q, kappa, and lambda light chains — showed trace mesangial granular staining. No dominant or codominant immune complex pattern was identified.

Impression

Non-proliferative glomerular morphology with low-intensity (trace) mesangial immune deposits on DIF. The pattern is most consistent with minimal change disease (MCD) in the clinical context, with early HIVAN remaining a differential diagnosis. The low-intensity pauci-immune mesangial staining and non-proliferative

morphology also raise the possibility of an autoimmune/SLE-related aetiology, which requires clinical and serological exclusion (ANA, anti-dsDNA).

Clinical Correlation and Management

Further workup including ANA, anti-dsDNA, complement levels, and urine microscopy was recommended to exclude lupus nephritis. The ongoing response to prednisolone was consistent with MCD. HAART was continued. Electron microscopy (EM) was recommended for definitive characterisation of podocyte foot process effacement and to exclude early membranous deposits.

Case D — Diabetic Nephropathy (Class III) with Nodular Glomerulosclerosis

Clinical Presentation

Patient 4 was a 43-year-old male with a known history of type 2 diabetes mellitus (T2DM) and hypertension, HIV reactive, on alternative medicines. He presented with bilateral pedal oedema. Investigations revealed a markedly elevated serum creatinine of 6.1 mg%, indicating advanced chronic kidney disease, with a 24-hour urinary protein of 4.6 g (nephrotic-range proteinuria). He was also found to be HIV reactive.

Biopsy Findings

Light Microscopy: Sections stained with H&E, PAS, MT, silver methenamine, and Congo red sampled a renal cortical parenchymal core containing up to 17 glomeruli, of which 8 (47.05%) were globally sclerosed/solidified. The remaining viable glomeruli showed significant mesangial matrix expansion. Peripheral capillaries appeared rigid but did not exhibit membrane texture alterations or mottling on silver methenamine staining. A few glomeruli revealed segmental tuft sclerosis, adhesions, and intraglomerular foam cell change. There was no evidence of tuft necrosis, crescent formation, intracapillary thrombi, or Congophilic glomerular deposits. Tubular atrophy and interstitial fibrosis involved approximately 35–40% of sampled cortex. Tubules showed thickened basement membranes, focally prominent cytoplasmic vacuolar change, and patchy acute injury. A few inspissated hyaline and granular casts were present in tubular lumina. Focal mild chronic interstitial inflammation was noted. Arteries showed marked medial thickening, subintimal sclerosis, and focal mucoid change. Arterioles revealed thickening of walls and diffuse subendothelial/transmural hyalinosis lesions.

Direct Immunofluorescence (DIF): Tissue included renal medulla and cortical parenchyma containing up to 3 glomeruli. IgA, IgM, C1q, kappa, and lambda light chains were negative. IgG showed patternless/smudgy staining along tubular and glomerular basement membranes. C3 showed focal entrapment. These findings are consistent with non-specific trapping rather than immune complex deposition.

Impression

Diabetic nephropathy (Class III — diffuse and nodular diabetic glomerulosclerosis) in the setting of clinical and laboratory evidence of diabetes mellitus and HIV co-infection. Additionally, focal mild chronic interstitial inflammation, patchy acute injury of viable cortical tubules, and moderate tubulointerstitial chronicity were observed. Prominent diffuse arteriolar hyalinosis with variable luminal compromise and arterial fibrointimal sclerosis were noted.

Clinical Correlation and Management

The findings were consistent with advanced diabetic nephropathy superimposed on a background of HIV infection. Optimisation of glycaemic and blood pressure control was prioritised. Renin-angiotensin-aldosterone

system (RAAS) blockade was recommended. HAART was initiated/continued. The patient was counselled regarding the high risk of end-stage renal disease (ESRD) and referred for nephrology follow-up with consideration of renal replacement therapy planning.

Discussion

This case series illustrates the remarkable histopathological heterogeneity of renal disease in HIV-positive individuals attending a tertiary nephrology centre in Northeast India. Across four biopsies, we identified four entirely distinct diagnoses — primary membranous nephropathy, acute tubular injury, non-proliferative glomerulopathy, and diabetic nephropathy — none of which were classical HIVAN. This finding reinforces the importance of histological characterisation rather than empirical diagnosis in this population.

HIVAN, characterised by collapsing FSGS with microcystic tubular dilation and heavy proteinuria, has traditionally been regarded as the archetypal renal lesion in HIV-positive individuals, particularly those of Black African ancestry.[1] However, the epidemiology of HIV-related renal disease has evolved considerably with the widespread use of HAART, and population-based studies now demonstrate that non-HIVAN lesions — including immune complex glomerulonephritis, membranous nephropathy, and comorbidity-related nephropathies — constitute a substantial proportion of renal diagnoses in HIV-positive patients.[2]

Case A represents a particularly instructive example. The combination of diffuse capillary wall IgG (dominant IgG4 subclass) granular deposits and strongly positive PLA2R staining establishes primary membranous nephropathy as the diagnosis with high confidence. PLA2R is expressed on the surface of podocytes and serves as the target antigen in approximately 70–80% of cases of primary MN; its tissue positivity by IHC or elevated serum anti-PLA2R titres are diagnostically specific.[3] The co-incidental HIV infection in this patient was not causally related to the renal lesion, and the histological distinction has major therapeutic implications — immunosuppression with rituximab or cyclophosphamide-based regimens is indicated for primary MN, whereas HIV-related MN may respond to HAART intensification.

Case B highlights drug-induced acute tubular injury, a well-recognised complication of antiretroviral therapy. Tenofovir disoproxil fumarate (TDF), a widely used component of first-line HAART regimens, is a well-documented nephrotoxin that can cause proximal tubular dysfunction (Fanconi syndrome) and frank ATI, particularly in the setting of pre-existing renal impairment.[4] Non-proliferative glomerular morphology in this context excludes primary glomerulonephritis and HIVAN, and the management priority is identification and substitution of the offending agent with tenofovir alafenamide (TAF), which has a superior renal safety profile.

Case C presents a diagnostically challenging non-proliferative glomerulopathy with low-intensity trace mesangial immune deposits. The partial response to corticosteroids, subnephrotic proteinuria, and non-proliferative LM morphology are most consistent with minimal change disease (MCD), which, though classically a disease of children, occurs in HIV-positive adults and may represent an immune dysregulation phenomenon.[5] However, the trace pauci-immune mesangial staining also raises the differential of early HIVAN and lupus nephritis (particularly Class II mesangial lupus), necessitating ANA/anti-dsDNA serology and ideally electron microscopy for definitive

diagnosis. The importance of electron microscopy in characterising foot process effacement and excluding subepithelial deposits cannot be overstated in such diagnostically ambiguous cases.

Case D illustrates the increasing prevalence of metabolic comorbidities — particularly T2DM — in the aging HIV-positive population. The histological features of Class III diabetic nephropathy with global glomerulosclerosis, nodular mesangial expansion (Kimmelstiel-Wilson nodules), and severe arteriolar hyalinosis, in the context of a serum creatinine of 6.1 mg% and nephrotic-range proteinuria, indicate advanced nephropathy with limited reversibility.[6] HIV infection itself may accelerate the progression of diabetic nephropathy through direct podocyte injury and chronic inflammatory mechanisms, though distinguishing additive from synergistic effects remains a subject of ongoing investigation. Management in such patients requires multidisciplinary coordination encompassing glycaemic optimisation, RAAS blockade, and preparation for renal replacement therapy.

Taken together, these cases emphasise that the renal biopsy retains indispensable diagnostic value in HIV-positive patients. Histology-directed therapy — rather than empirical HAART optimisation alone — is likely to improve patient outcomes and avoid unnecessary immunosuppression in cases where it is not indicated (e.g., drug-induced ATI) or delay it in cases where it is (e.g., primary MN).

Table 1: Summary of Cases

Case	Patient	Age / Sex	ART Status	S. Creatinine	24h Urine Protein	Histopathological Diagnosis
A	Patient 1	38 yr / M	On HAART	1.17 mg%	2.9 g/day	Membranous glomerulopathy (PLA2R+)
B	Patient 2	48/male	On HAART	3.2 mg/dl	0.8g/day	Acute tubular injury (drug-induced / ischemic)
C	Patient 3	47 yr / F	On HAART (since 2014)	0.9 mg%	0.3 g/day (on pred.)	Non-proliferative glomerulopathy; trace mesangial immune deposits (MCD vs. early HIVAN; SLE to exclude)
D	Patient 4	43 yr / M	HIV reactive	6.1 mg%	4.6 g/day	Diabetic nephropathy (Class III) with nodular glomerulosclerosis

Pred. = prednisolone; MCD = minimal change disease; HIVAN = HIV-associated nephropathy; SLE = systemic lupus erythematosus; LM = light microscopy; DIF = direct immunofluorescence; IHC = immunohistochemistry

Conclusion

Renal disease in HIV-positive patients encompasses a broad histopathological spectrum extending well beyond classical HIVAN. Our case series demonstrates that primary membranous nephropathy (PLA2R-positive), drug-induced acute tubular injury, non-proliferative

glomerulopathy, and diabetic nephropathy can all occur in HIV-infected individuals. Accurate histological diagnosis through renal biopsy is essential to guide appropriate, disease-specific management. Clinicians should maintain a low threshold for renal biopsy in HIV-positive patients with unexplained renal dysfunction or proteinuria, particularly given the implications for immunosuppressive therapy versus HAART modification. Collaborative nephrology and infectious disease management is pivotal to optimising outcomes in this complex patient population.

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