Uncommon presentation of common Diseases

Dr Swati Gohel
Consultant Infectious Diseases
Sarathi – Centre for infectious diseases(SCID)
Narayana multispecialty hospital, Ahmedabad

Case# Dec'2022

72yr/Male/farmer/Anand(Gujarat) – (brought by distant relatives/care taker!)

Presented to Nephrology unit

- Bilateral lower limb swelling
- Weight gain 12kg
- Occasional episodes of hematuria

} 2 months

-no fever/cough/chest pain/orthopnoea,

-no burning micturition/decreased urine output)

Past medical history:

- Diabetes mellitus type 2 - 30 yrs (retinopathy and neuropathy)
- Hypertensive – 6 yrs
- Morbid obesity (BMI-39) (?OSA)
- IHD- s/p PTCA -2017

- Retrovirus positive -2017 on ART from Govt sector (TDF/3TC/DTG)
  (baseline CD4 count ->250cells/cumm,
  HIV viral-NA)

- Wife – HIV -negative

Examination

- Pallor +
- Bilateral Pitting Pedal edema up to knee
- P- 70/min
- BP – 106/70
- Rest systemic exam – bilateral basal crepts
- No peripheral lymphadenopathy, No rash , No oral or genital ulcers

	6/12	7/12	23/12	23/01/23
Hb (gm/dl)	9.6	10.2		
Tc (N/L/M/E)(cells/ul)	6670 (53/18/20/06)	6280 (54/24/14/4.8)		
Platelets (cells/ul)	2.11	3.11		
Bilirubin		0.43		
SGPT (IU/L)		24.9		
Pt INR	1.02			
Total protein (gm/dl)(6-8)	6.93	7.27		
Albumin (3.5-5.5)	3.01	3.13		
Globulin	3.92	4.14		
Creatinine (mg/dl)	1.48	1.55		
PSA		0.004		
Sodium (meq/l)	136			
Potassium(meq/l)	3.95			

URINE ANALYSIS

Urine Routine		
Colour-UR	Deep Yellow	U/L
Appearance-UR	Slight Turbid	
pH-UR	6.0	
Sp.Gravity-UR	1.030	
Protein-UR	+ 3	
Sugar-UR	+ 2	
WBC-UR	20-25	
RBC-UR	>100	
Epithelial Cells-UR	5-10	U/L
Casts-UR	Granular 2-5/ LPF, Hyaline 0-2/ LPF, Waxy OCC/ LPF	
Crystals-UR	Absent	
Other findings-UR	Bacteria, 10 % Dysmorphic RBC	

- C3 level- 70.2 (90-180),
- chest x ray – bilateral minimal pleural effusion
- CRP- 30.8 (0-6)

- HBsAg – Neg
- Anti HCV – neg
- Urine albumin creatinine ratio-elevated
- **24hour urinary protein -7gm/dl**
- Anti PLA2R <2 (negative)

- **Nephrotic syndrome**

Pat Type	**Special Nephrology**
Date & Time	**06/12/2022 10:39 AM**

USG: Abdomen

Rt. Kidney : 10.9 x 5.1 CM.
Mild increase in echogenicity of cortex.
Maintained C.M.Differrentiation.
No calculus /hydronephrosis seen.
Right side RI – .75

Lt. kidney : 10.2 x 4.9 CM.
Mild increase in echogenicity of cortex.
Maintained C.M.Differrentiation.
No calculus /hydronephrosis seen.
Left side RI – .75

Urinary bladder is empty.

Liver show grade I fatty changes. No SOL seen.

Biliary / portal radicles are normal.
Gall bladder – show sludge.
Pancreas & Spleen - Normal appearances.
Bilateral minimal pleural effusion seen.
Ascites – Not seen

Immuno-Fluorescence : 12 glomeruli (3 sclerosed)

IgA : negative

IgG : Positive coarse granular along capillary wall +3.

IgM : Negative

C3 : Positive coarse granular along capillary wall +1.

C1q : Positive coarse granular along capillary wall +1.

Kappa : Positive coarse granular along capillary wall +1.

Lambda : Positive coarse granular along capillary wall +2.

PLA2R (IHC) : Negative.

Light Microscopic Examination : (HE, PAS, PASM, Trichrome)

22 glomeruli included in single core of renal tissue.

1 glomerulus globally sclerosed.

Remaining glomeruli show mild focal increase in mesengial matrix with

- Cells : Normal.

Capillary lumina : Patent.

Capillary loops are thickened.

Basement membrane is thickned & shows spikes.

Tubules show atrophy +1.

Interstitium shows patchy cell infiltrate & fibrosis +1.

Blood vessels show moderate myointimal proliferation & arteriolar hyalinosis

Diagnosis :

- **Membranous Nephropathy.**

Pt ref for ID consultation for

- Change of ART in view of renal involvement
- Clearance for immunosuppression (rituximab) for membranous nephropathy

- ID diagnosis

1)HIV positive – to check virological and immunological status

2)Membranous nephropathy –switch to Abacavir based regimen

-to rule out OI before clearance for immunosuppressant

HIV work up

CD4 CD8 COUNT

Specimen: EDTA/Heparin blood, Method: Flowcytometry

Four colour antibodies CD45 FITC/CD4 RD1/CD8 ECD/CD3 PC5 incubated with whole blood. A tetra CXP-system provides automated analysis of lymphocyte subpopulations.

WBC COUNT		6290	/cmm	4000 - 10000
LYMPHOCYTE %		25.5	%	
CD3 % (T cell)		62.6	%	60 - 85
CD4 % (Helper T cell)	L	**28.4**	%	30 - 65
CD8 % (Cytotoxic T cell)		30.1	%	10 - 35
ABSOLUTE LYMPHOCYTE COUNT		1604	/cmm	1000 - 3000
ABSOLUTE CD3 (T cell)		1004	/cmm	600 - 2500
ABSOLUTE CD4 (Helper T cell)		456	/cmm	400 - 1500
ABSOLUTE CD8 (Cytotoxic T cell)		483	/cmm	200 - 1100
CD4/CD8 RATIO		0.94		0.7 - 3.5

Sample Type: EDTA Whole Blood

Note:
Absolute count is counted by two stage method.

MOLECULAR

Parameter	Result	Units	Biological Reference Interval
PCR HIV QUANTITATIVE (VIRAL LOAD)	Target Not Detected	IU/mL	

Taqman Probe based Real Time PCR

Sample Type: EDTA Whole Blood

Note:
HIV-1 viral load is expressed in IU/ML. The linear range of this assay is 100 HIV-1 RNA IU/ml to 1,00,00,000 HIV-1 RNA IU/ml. Calculated copy numbers less than 100 IU/ml or above 1,00,00,000 IU/ml will be reported as either <100 or>1,00,00,000 IU/ml.

HLA B*57:01 – detected

Questions

- What is the cause for membranous nephropathy (Idiopathic or secondary)?
- What ART to be considered in view of AKI and risk of Abacavir hypersensitivity?
- Clearance for immune suppression!

Anything missed?

Causes of renal involvement in HIV

Acute kidney injury

- Drugs (tenofovir, atazanvir, Bactrim, acyclovir)
- Infection
- HIVAN (HIV associated nephropathy)

  Predominantly seen among African American patients

  -High viral loads and

  -low CD4 counts
- Alternative ART?

Chronic kidney diseases

- **HIVAN**

Immune complex kidney disease

- Membranous nephropathy,
- Membranoproliferative and mesangial proliferative glomerulonephritis,
- “Lupus-like" proliferative glomerulonephritis
- Immunoglobulin A (IgA) nephropathy

Glomerulonephritis due to hepatitis C virus coinfection

- Syphilis antibody – TPHA -positive
- VDRL – 1:8 titre

Idiopathic

Secondary Solid malignant tumors,
Medications (eg, penicillamine, gold, NSAIDS)
Autoimmune diseases (eg, lupus, rheumatoid arthritis, mixed connective tissue disease)
Infections (eg, hepatitis B, hepatitis C, **syphilis**)

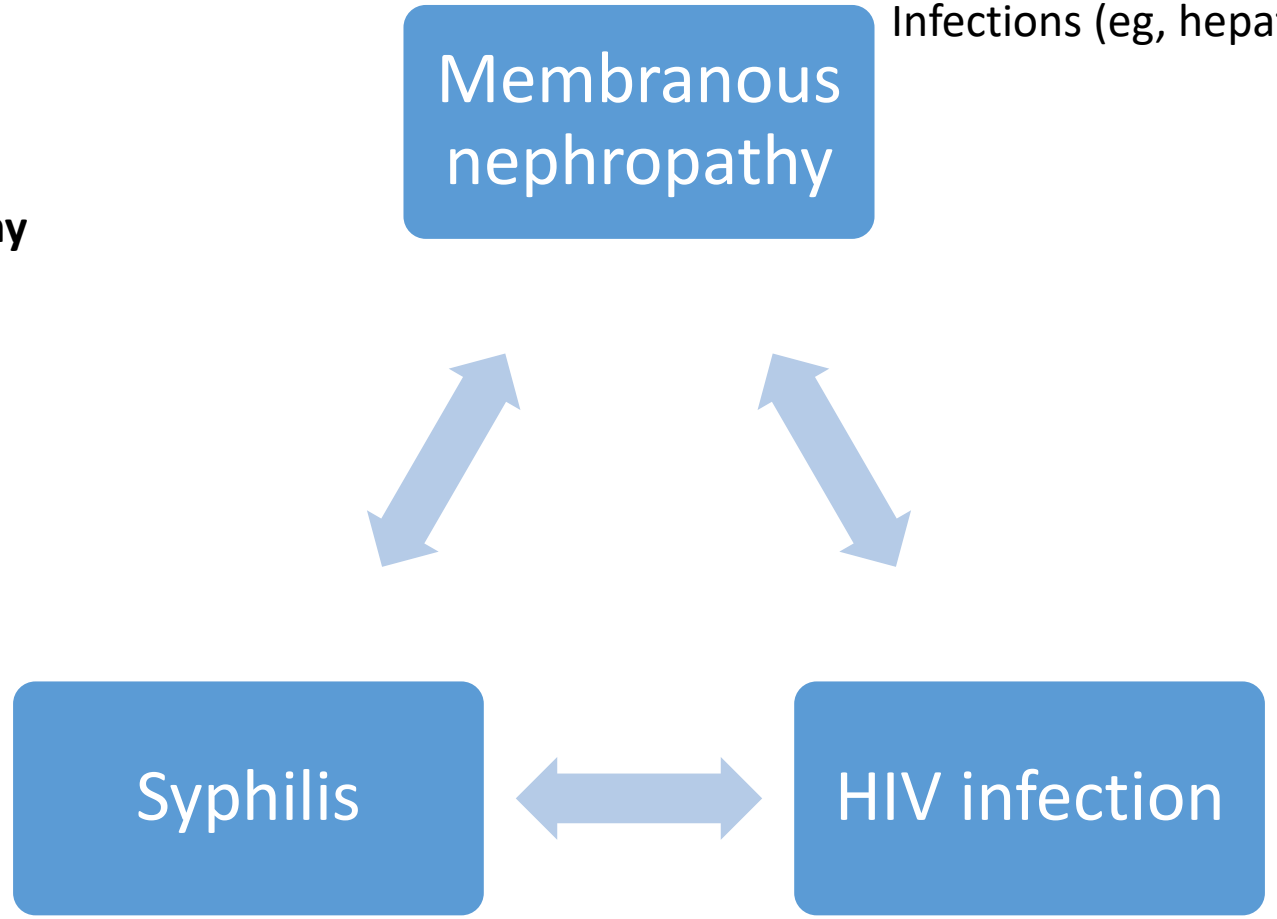
Renal Manifestations of Syphilis

Glomerular
- ✓ Minimal change disease/focal sclerosis
- ✓ **Membranous nephropathy**
- ✓ Crescentic glomerulonephritis
- ✓ Postinfectious glomerulonephritis
- ✓ Amyloidosis

Tubular
- ✓ Acute tubular necrosis
- ✓ Interstitial nephritis

Vascular
- ✓ Renal artery stenosis
- ✓ Endarteritis

Mass lesion
- ✓ Renal gumma



- Can syphilis lead to membranous nephropathy? (can we establish causal relationship!)
- Can treatment of syphilis reverse nephropathy?
- Literature review!!!

Nephrotic syndrome in HIV

- **HIV-associated nephropathy (HIVAN)** - characterized by collapsing focal and segmental glomerulosclerosis and acute interstitial nephritis with microcystic tubular dilatation

  -Predominantly seen among African American patients

  -High viral loads and low CD4 counts

- Nephrotic syndrome in patients with HIV may be caused by any number of glomerular pathologies

  -Immune complex glomerulonephritis,

  -Minimal change disease, and

  -Immunoglobulin A (IgA) nephropathy

Renal manifestations of syphilis

- **Membranous nephropathy** is the **most common glomerular lesion**

- Circulating immune complexes have been seen among patients with **secondary syphilis** and immune complexes containing antitreponemal antibodies have been eluted from renal biopsy specimens.

- As opposed to idiopathic membranous nephropathy, where IgG and C3 staining are typically seen by immunofluorescence studies on renal biopsies, membranous nephropathy secondary to syphilis typically has staining not only for IgG and C3, but also occasionally with IgA, IgM, and C1q ("**full house pattern**")

CLINICAL MEDICINE

Secondary Syphilis Associated with Membranous Nephropathy and Acute Hepatitis in a Patient with HIV: A Case Report

Zhou Zhang, MD; Aviv Hever, MD; Nitin Bhasin, MD; Dean A Kujubu, MD

Perm J 2018;22:17-062

E-pub: 12/13/2017

https://doi.org/10.7812/TPP/17-062

ABSTRACT

Introduction: We present a case of membranous nephropathy associated with a secondary syphilis infection in a patient with HIV.

Case Presentation: A 37-year-old white man with HIV who was receiving highly active antiretroviral therapy presented to the Emergency Department with 6 weeks of rectal pain. He had a CD3-CD4 count of 656 cells/mm^3 and an undetectable viral load. On admission, he was found to have an anal ulcer, a serum creatinine of 1.4 mg/dL (baseline 0.7 to 1.0 mg/dL), elevated transaminases, positive rapid plasmin reagin, and a urine protein/creatinine ratio revealing nephrotic-range proteinuria. Renal biopsy demonstrated membranous nephropathy with features suggestive of a secondary cause. Our patient was treated with penicillin for secondary syphilis, with normalization of renal function, resolution of the nephrotic syndrome, and improvement of his elevated transaminases.

Discussion: This case is a reminder that patients with HIV are not infrequently coinfected with *Treponema pallidum* and that secondary syphilis can have systemic manifestations, including elevated transaminases and nephrotic syndrome. Prompt diagnosis and treatment will result in resolution of these problems.

status.[6] In 2010, Horberg et al[7] examined the Kaiser Permanente Northern California patient population and reported that the adjusted incidence rate ratio on syphilis infection in HIV vs non-HIV-infected individuals was 86.0, and that this ratio increased with time.

Nephrotic syndrome is well known to be associated with HIV infection. Although the disease entity termed HIV-associated nephropathy (HIVAN), which is characterized by collapsing focal and segmental glomerulosclerosis and acute interstitial nephritis with microcystic tubular dilatation, is predominantly seen among African American patients with high viral loads and low CD4 counts,[8] nephrotic syndrome in patients with HIV may be caused by any number of glomerular pathologies, including immune complex glomerulonephritis, minimal change disease, and immunoglobulin A (IgA) nephropathy, among others.[9,10] Thus, it would be a mistake to assume that all nephrotic syndromes presenting in an HIV-positive patient is necessarily caused by HIVAN. This is particularly true if the patient is coinfected with either syphilis, hepatitis B, or hepatitis C, each of which may cause other distinct glomerular diseases.

The following case serves as a reminder that nephrotic syn-

- ✓ Young male
- ✓ HIV – virologically and immunologically well controlled

- ✓ Documented exposure
- ✓ Clinical features of **secondary syphilis**
- ✓ Liver and kidney involvement
- ✓ Membranous nephropathy on kidney biopsy

- ✓ **Rapid reversal of kidney and liver function after benzathine penicillin**

Published in final edited form as:
Sex Transm Dis. 2019 December ; 46(12): 816–818. doi:10.1097/OLQ.0000000000001062.

Syphilis-associated acute renal failure and hepatitis in the setting of HIV co-infection

Michael Sciaudone, MD, **Sarah Rutstein, MD, PhD**, **Claire E. Farel, MD, MPH**
University of North Carolina at Chapel Hill Division of Infectious Diseases

Abstract

Two individuals with HIV presented in acute renal failure with nephrotic range proteinuria and were diagnosed with secondary syphilis. One of them also had elevated transaminases. Kidney biopsies revealed membranous nephropathy, a rare complication of secondary syphilis, in both cases. Normal hepatic and renal function were restored after treatment with penicillin.

Summary:

In the context of increasing rates of primary and secondary syphilis, clinicians will be more likely to encounter unusual manifestations of this disease. Here we describe two patients with syphilitic nephropathy, one of whom had concomitant hepatitis.

Nephrology Reviews 2012; volume 4:e10

Syphilis and kidney disease: a case report and review of literature

Bashar Hannawi,[1] Rajeev Raghavan[2]

[1]Department of Medicine, the Methodist Hospital, Houston; [2]Department of Medicine and Division of Nephrology, Baylor College of Medicine, Houston, USA

Abstract

There has been a resurgence in the number of incident cases of syphilis in the United States. Syphilis can affect the kidney and usually causes a glomerular lesion with variable amounts of proteinuria. We present a case of a 24-year old African-American male who presented with both membranous glomerulonephritis and secondary syphilis. His kidney disease resolved after a course of penicillin. Recognizing the association of syphilis and proteinuria is important since antibiotic therapy generally results in complete recovery of the associated nephropathy.

Introduction

Syphilis is the *great imitator* of disease. It is caused by the bacterium *Treponema Pallidum* and remains an elusive condition to diagnose. Syphilis is a relatively uncommon disease in the United States but its incidence has dramatically increased since 2000.[1] Syphilis is clinically subdivided into three stages: primary (a painless chancre at an inoculation site), secondary (rash, lymphadenopathy and constitutional symptoms), and tertiary (cardiovascular or central nervous system involvement). There is a latency period of variable duration between the first two stages.

Kidney involvement due to syphilis has been reported during secondary, latent and tertiary syphilis. Fewer than 20 cases of *renal*

glasses of wine per week and has smoked 0.5 packs of tobacco daily for five years. His last sexual encounter had been approximately a month previously with a male. No family history of renal disease was requested. His physical examination on admission was normal except for a 1+ pitting edema below the waist, a penile chancre and small hyperpigmented macules on his legs. Pertinent laboratory data included hemoglobin 10.9 mg/dL, blood urea nitrogen 8 mg/dL, creatinine 1.1 mg/dL and serum albumin 1.3 mg/dL (with total protein level 4.4 mg/dL). Iron studies showed ferritin of 250 ng/mL, serum iron 41 µg/dL, TIBC 153 µg/dL, iron saturation 27%; these indices suggest an acute phase response. Vitamin B12 and red blood cell folate levels were normal.

Serum concentration of electrolytes, calcium (corrected to albumin level), bilirubin, thy-

DOI 10.1007/s11255-011-9945-6

NEPHROLOGY – CASE REPORT

An unusual cause of membranous glomerulonephritis in a patient with HIV

Ying Maggie Chen · Luis A. Marcos · Helen Liapis · Thomas H. Steinberg · Aubrey R. Morrison

Received: 3 January 2011 / Accepted: 10 March 2011 / Published online: 25 March 2011

Abstract A 68-year old Caucasian male with a past medical history of human immunodeficiency virus (HIV) infection presented with acute oliguric renal failure and maculopapular rash. Renal biopsy demonstrated extensive foot process effacement as well as confluent small subepithelial electron-dense deposits, which is diagnostic of membranous glomerulonephritis. Subsequent serological tests showed venereal

Keywords Acute kidney injury · Human immunodeficiency virus · Membranous glomerulonephritis · Syphilis

Case presentation

A 68-year old Caucasian male with a history of

- ✓ Elderly male
- ✓ HIV coinfection
- ✓ Virologically and immunologically well controlled
- ✓ Maculopapular rash over trunk

- ✓ Neurosyphilis and membranous nephropathy

- ✓ Complete reversal of renal injury with penicillin

Qi et al. BMC Nephrology (2021) 22:196
https://doi.org/10.1186/s12882-021-02404-z

BMC Nephrology

CASE REPORT Open Access

Syphilis-related rapidly progressive glomerulonephritis: a case presentation

A. Qi[1], P. O. Fiset[2] and L. Pilozzi-Edmonds[1*]

Abstract

Background: Syphilis is a multisystemic infection that causes a wide variety of symptoms and thus has been dubbed one of the great medical mimickers. Due to recent global re-emergence of syphilis, it has become important to recognize its various presentations. Relative to the kidney, syphilitic infections generally present themselves with nephrotic range proteinuria, and are most often associated with pathological features of a membranous glomerulonephritis with subepithelial immune complex deposition. However, other rare renal presentations have been reported. One of these includes a rapidly progressive glomerulonephritis picture. All described cases have been successfully resolved with the treatment of the underlying syphilis infection.

Case presentation: The patient was an elderly woman of Caribbean descent who presented with lower extremity weakness, anasarca and proteinuria, hematuria with progressive renal failure. On kidney biopsy, she was found to have a pauci-immune crescentic glomerulonephritis pattern and a concomitant acute tubulointerstitial nephritis. She had a positive *Treponema pallidum* particle agglutination test and a negative syphilis rapid plasma reagin test with clinical evidence of polyneuropathy suggestive chronic syphilis infection.

Conclusion and discussion: It is important in the context of pauci-immune crescentic glomerulonephritis to explore all differential diagnoses. Given the positive syphilis serologies, clinical context and presence of tubulointerstitial nephritis, she was determined to have syphilitic glomerulonephritis that resolved with a course of both penicillin and steroids.

Original Article

Kidney Disease in Human Immunodeficiency Virus-seropositive Patients: Absence of Human Immunodeficiency Virus-associated Nephropathy was a Characteristic Feature

Abstract

Human immunodeficiency virus (HIV) infection can cause a broad spectrum of renal diseases. However, there is paucity of Indian data on the patterns of renal lesions in HIV-seropositive patients. The aim of the present study was to delineate the spectrum of renal lesions in HIV/acquired immunodeficiency syndrome patients. In this prospective study, all HIV-positive patients of both genders aged >18 years were screened for renal disease. Patients with proteinuria of more than 1 g/24 h were subjected to renal biopsy. A total of 293 HIV-positive patients were screened; of these, 136 (46.4%) patients found to have renal involvement. Dipstick-positive proteinuria of 1+ or more was observed in 112 (38.2%) patients, and 16 (14.2%) patients had proteinuria of more than 1 g/24 h. Renal biopsy in 14 cases revealed glomerulonephritis (GN) in 12 (85.7%) (isolated GN in 4 [28.5%] and GN mixed with chronic TIN in 8 [57.1%]) patients. These include mesangioproliferative GN in 5 (35.7%), membranoproliferative GN in 2 (14.2%), focal segmental glomerulosclerosis in 2 (14.2%), diffuse proliferative GN in 2 (14.2%), and diabetic nephropathy in 1 (7.1%) patients. Chronic interstitial nephritis was noted in 10 (71.42%) (superimposed on GN in 8 [57.1%], isolated in 2 [14.2%]) patients. Granulomatous interstitial nephritis was seen in 3 (24.1%) cases. GN and chronic interstitial nephritis were noted in 85.7% and 71.42% of patients, respectively, mostly superimposed on each other. Mesangioproliferative GN was the most common glomerular lesion, but classical HIV-associated nephropathy was not observed.

Keywords: *HIV-associated nephropathy, HIV infection, nephropathies, proteinuria*

J. Prakash,
V. Ganiger,
S. Prakash[1],
M. Sivasankar,
S. Sunder[2],
U. Singh[3]

Departments of Nephrology, [2]Medicine and [3]Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, [1]Department of Medicine, TNMC, Mumbai, Maharashtra, India

Prakash J, Ganiger V, Prakash S, Sivasankar M, Sunder S, Singh U. Kidney disease in human immunodeficiency virus-seropositive patients: Absence of human immunodeficiency virus-associated nephropathy was a characteristic feature. Indian J Nephrol 2017;27:271-6.

Back to the case! – Christmas cake

- Can syphilis lead to membranous nephropathy? (can we establish causal relationship!) - **YES**

- Can treatment of syphilis reverse nephropathy? – **YES**

- Pt was started on weekly Benzathine penicillin and showed dramatic improvement on follow up 1 week (improvement in creatinine and proteinuria)

- Patient was started on TAF/FTC/DTG

Last follow up after 4 weeks of initial presentation –significant reduction in proteinuria and creatinine normalized

	6/12	7/12	23/12	23/01/23
Hb (gm/dl)	9.6	10.2	10.9	
Tc (N/L/M/E)(cells/ul)	6670 (53/18/20/06)	6280 (54/24/14/4.8)	9855	
Platelets (cells/ul)	2.11	3.11	2.5	
Bilirubin		0.43		
SGPT (IU/L)		24.9		
Pt INR	1.02			
Total protein (gm/dl)(6-8)	6.93	7.27		
Albumin (3.5-5.5)	3.01	3.13		
Globulin	3.92	4.14		
Creatinine (mg/dl)	1.48	1.55	1.32	1.09
PSA		0.004		
Sodium (meq/l)	136			
Potassium(meq/l)	3.95			

Take home message

- Nephrotic syndrome in a patient with HIV may not necessarily be caused by the HIVAN especially in the era of HAART

- Syphilis is a very important and completely reversible cause for membranous nephropathy