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Clinical illustration

THE KIDNEY'S DOUBLE JEOPARDY: GLOMERULAR AND TUBULAR DYSFUNCTION IN HIV INFECTION.

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ABSTRACT

Patients with Human Immunodeficiency Virus (HIV) disease face a heightened risk of various kidney diseases including HIV-associated nephropathy (HIVAN), HIV immune complex kidney diseases (HIVICK) and drug-related kidney damage. Tubular dysfunctions

have been described in the background of HIV infection but not routinely screened for in clinical practice. This tubular dysfunction has been ascribed to direct effect of HIV infection or its treatment. Co-existence of both glomerular and tubular dysfunction represent a twin attack on the kidneys and rarely described in literature. This was a 38-year old woman with chronic kidney disease due to human immunodeficiency virus (HIV) infection. There were clinical and laboratory evidence suggestive of HIV-associated nephropathy and proximal renal tubular dysfunction. This case was chosen for presentation to highlight that HIV infection and disease is a common cause of chronic kidney disease, some patients have co-existent tubular dysfunction, and outcome of treatment can be good with institution of appropriate anti-retroviral medications.

INTRODUCTION

Chronic kidney disease is a frequent complication of HIV infection, occurring in 3.5-48.5%,[1] and occurs as a consequence of therapy of HIV infection and its complication. In Nigeria, studies conducted reported prevalence of renal disease in HIV of 38% in a multi-centre study involving two tertiary hospitals in Ile Ife and Port Harcourt, [2] 56.8% in Kano,[3] 23.8% in Jos,[4] 53.3% in Benin [5] and 28.9% in Ibadan.[6] This shows that renal disease from HIV is prevalent in Nigeria. The classic involvement of the kidney by HIV infection is HIV-associated nephropathy (HIVAN), occurring typically in young adults of African ancestry with advanced HIV disease in association with APOL1 high-risk variants.[7] Renal biopsy is necessary for this diagnosis because there are other HIV-related diseases that present like HIVAN, clinically and laboratory-wise, and therapy differs.

CASE PRESENTATION

The index patient was a 38 year old secondary school teacher diagnosed of human immunodeficiency virus (HIV) infection 3 years earlier and started on Tenofovir-based anti-retroviral medications. She was however non compliant with medications and clinical visit. She presented to the accident and emergency unit of our hospital with facial and bilateral leg swelling of 4 months duration, fever and dysuria of 5 days duration. He was apparently well until 4 months prior to presentation when she developed facial and bilateral leg swelling of 4 months duration. The facial swelling was worse in the morning and regressed as the day progressed. The leg swelling started about the same time and progressed to the upper one-third of the legs. There was no history of orthopnea or paroxysmal nocturnal dyspnoea. No history of palpitations or chest pain. There was history of pains and difficulty swallowing but no history of jaundice, abdominal swelling or abdominal pains. There was associated anorexia, easy fatigability and progressive weight loss. Five days before presentation, she developed high grade fever with associated dysuria, nocturia and passage of frothy urine. There was a history of lower abdominal pain. There was associated restlessness but no neck stiffness or neck pains and no loss of consciousness. She is not a previously

diagnosed hypertensive, diabetic or sickle cell disease patient and no family history of kidney diseases. She did not have chronic cough in the past. Her CD4 count at diagnosis of HIV was 314cells/µl. She had been on Tenofovir-based antiretroviral drugs (Tenofovir 300mg o.d, Lamivudine 300mg b.d and Efavirenz 600mg nocte), although she was not adherent to these drugs due to fear of possible side effect. She takes herbal medications occasionally, no history of chronic ingestion of non steroidal anti-inflammatory drugs or use of mercury-containing cosmetics. No history of smoking of tobacco in any form or alcohol intake. She was married in a monogamous setting with 2 children and the husband died 2 years ago from HIV disease. There was no history of sexual relationship with anyone aside her husband before and after his death.

EXAMINATION

General examination revealed a young woman, febrile (38.8^0C), pale, not dehydrated, no finger clubbing, with oral thrush. There was minimal bilateral pitting oedema of the lower limb up to mid-leg No significant peripheral lymphadenopathy or finger clubbing. Her weight was 56kg. Cardiovascular system examination revealed a pulse of 72beats per min, regular and normal volume. Blood pressure was 130/80mmHg and JVP was not elevated. Apex beat was not displaced and the heart sounds were normal 1^{st} and 2^{nd} heart sounds. Respiratory rate was 24 cycles per minute with normal vesicular breath sounds. The abdomen was full, moved with respiration, there was no area of tenderness and the organs were not palpably enlarged. She was conscious but confused, not oriented in time, place and person. No meningeal irritation and no neck stiffness. There was flapping tremor of outstretched hand.

The provisional diagnoses were Acquired Immunodeficiency Syndrome (AIDS) with
-acute on chronic kidney disease precipitated by urinary tract infection
-oropharyngeal candidiasis
Patient was admitted into the ward and the following investigations were performed - CD4 count, HIV viral load, abdominal ultrasound scan, spot urine protein: creatinine ratio, fasting lipid profile, serum protein, albumin and globulin, calcium, phosphate, full blood count, urine microscopy, culture and sensitivity, fasting blood sugar and fractional phosphate reabsorption

Her HIV viral load was 5,320 copies/ml. She was non-reactive to hepatitis B and anti hepatitis C antibody. Results of other investigations are as illustrated in table 1. The fractional tubular resorption of phosphate in the patient is 0.71.

Renal ultrasound; The kidneys measure 13.4 x 6.6cm and 14.1 x 5.6cm for left and right respectively. Both have increased echogenicity and complete loss of corticomedullary differentiation. No stone or cyst was seen.
Urine microscopy showed gram negative cocci. Culture yielded moderate growth of Escherichia coli sensitive to Ofloxacin^{+++}, Ciprofloxacin^{+}, Amoxicillin^{+}

TREATMENT
She received haemodialysis, IV frusemide 60mg every 12 hours, Tabs lisinopril 5mg daily, Tabs vitamin c 100mg every 8 hours, caps fluconazole 100mg every 12 hours. She was commenced on intravenous

ciprofloxacin 200mg twice daily till result of urine microscopy, culture and sensitivity was retrieved.
After all the results were retrieved, a further diagnosis of proximal tubular dysfunction secondary to tenofovir nephrotoxicity was made. The diagnosis of urinary tract infection was also confirmed and ciprofloxacin was changed to ofloxacin.

Further treatment included change of antiretroviral drug to Lamivudine –based combination. She was counseled on her condition. He was also given iron sucrose infusion 100mg in 250mls of normal saline twice weekly. Subcutaneous erythroproeitin 4,000 iu twice weekly and haematinics which include ferous sulphate 200mg every 12 hours, folic acid 5mg daily, selenium 200µg daily and vitamin B complex and calcium carbonate/vitamin D (calceaus) once daily. Patient improved remarkably after nine days in the hospital and three session of haemodialysis. The facial swelling and leg oedema resolved completely, her laboratory parameters also improved serially.

The nature and course of her renal disease was explained to her, and the treatment options which includes dialysis and renal transplant discussed with her. The need to have an arteriovenous fistula creation for haemodialysis was also discussed. She was discharged to the outpatient renal clinic after 11 days and following satisfactorily improvement in her condition. Laboratory investigations at discharge and follow up are as shown in table 2.

DISCUSSION

The index patient was diagnosed with HIV infection five years prior to this current admission with a low baseline CD4 count of 314cells/µl. At this presentation, she was found with low CD4 count, high viral load, evidence of renal damage (nephrotic-range proteinuria), proximal tubular dysfunction (reduced fractional tubular reabsorption of phosphate and normoglycemic glucosuria) as well as reduced renal function (GFR<60ml/min/1.73m^2). On radiological assessment, there were evidence in keeping with long-standing kidney disease (complete loss of cortico-medullary differentiation). Hence, the diagnosis of CKD secondary to HIV.

Kidney disease is a frequent complications of HIV infection, occurring in 3.5-48.5% and occurs as a complication of HIV infection and as a consequence of therapy of HIV infection and its complications.[1] The causes of renal diseases in HIV infected patients are multifactorial and include diarrheal illnesses, opportunistic infections or neoplasms, nephrotoxic agents for treating opportunistic infections such as foscarnet, amphotericin B, pentamidine, sulphadiazine, antiretroviral medications especially tenofovir, protease inhibitors such as indinavir or as a result of the direct cytopathic effect of the virus on kidney glomeruli.[8] The risk factors for kidney disease in HIV infection include;[2] race (worse in individuals of African descent), family history of chronic kidney disease, use of nephrotoxic agents (including traditional medicines), diabetes mellitus, hypertension, hepatitis C, CD4+ count < 200 cells/mm^3 and HIV viral load > 4000 copies/ml. The index patient had clear risk factors for kidney disease in

the background of HIV infection which were African descent, use of nephrotoxic medications (and tenofovir-based ART medication), low CD4+ count (97 cells/µl) and high viral load of 6,500copies/ml. Individuals of African descent are predisposed to HIV-associated nephropathy. Genetic variants of recent African origin might account for this susceptibility and was mapped by admixture linkage disequilibrium (MALD). A locus on chromosome 22 was found to have a strong association with HIV kidney disease in African-Americans.[7] Variants in APOL1, encoding apolipoprotein L1, accounted for most of this increased risk.[9] Ulasi *et al*.[10] had earlier documented that APOL1 genetic risk variants are common among Nigerians, and are also highly associated with non-diabetic CKD in this Nigeria including focal segmental glomerulosclerosis (FSGS).

The index patient was on tenofovir-containing HAART before the diagnosis of chronic kidney disease. While commencement of HAART increases outcomes in patients, tenofovir have been demonstrated to be toxic to the kidneys (especially the tubules) if dose adjustment is not properly done or it is continually been administered in patients with impaired GFR.[11] Functional abnormalities of the proximal tubule lead to decreased reabsorption of phosphate, increased secretion of uric acid, normoglycemic glucosuria and tubular proteinuria. Proximal tubular renal dysfunction can be determined on the basis of six criteria:[12]

- Glucosuria (urine glucose >300 mg daily) with normal glycaemia (plasma glucose <100 mg/dl);
- Hyper aminoaciduria (any amino acid in urine, with the exception of hystidine, glycine and serine);
- Fractional tubular resorption of phosphate [1-{(urine phosphate × plasma creatinine)/ (plasma phosphate × urine creatinine)] lower than 0.82;
- Total excretion of phosphate (urine phosphate × urine volume) greater than 1200 mg daily;
- Fractional excretion of uric acid [{(urine uric acid × plasma creatinine)/ (urine creatinine ×plasma uric acid)} ×100] greater than 15%; and
- β-2-microglobulinuria greater than 1 mg daily.

Decreased phosphate tubular reabsorption has been described as an early marker of proximal tubular alteration.[13] Proximal tubular renal dysfunction occurs when two or more of these parameters are present, with at least one of them being any of the fanconi syndrome defining alteration (glucosuria in non diabetic patients, hyperphosphaturia, or hyper aminoaciduria).[13] This patient had normoglycaemic glucosuria and decreased phosphate tubular reabsorption; hence was diagnosed to have proximal tubular dysfunction. Treatment involves withdrawal of the offending drug (tenofovir) which was done in this patient.

The index patient presented with nephrotic range proteinuria (protein: creatinine ratio of 2,450mg/g), minimal leg oedema, normal blood pressure, renal dysfunction (GFR of 11ml/min/1.73m^2) and enlarged kidneys on ultrasound. These findings were suggestive of HIV-associated

nephropathy and is the classic involvement of the kidney with HIV infection. It manifests clinically with proteinuria (usually in nephrotic range), renal dysfunction, normal/increased renal sizes and pathologically as a focal segmental glomerulosclerosis (FSGS) with collapsing glomerulopathy, microcystic tubular dilatation and interstitial inflammation.[14] It has been reported in 3.5-10% of HIV-infected population in the USA, predominantly in individuals of African ancestry with advanced HIV disease (as in this patient); though it may occasionally be diagnosed before acute HIV seroconversion.[15] It is a salt-loosing nephropathy, hence patients' usually have minimal edema (not comparable to the degree of proteinuria) and low or normal blood pressure.[16] The disease has rapid progression to end-stage renal disease (ESRD) without anti-retroviral therapy (ART). In this patient, renal biopsy was not obtained due to patients'refusal despite counseling on this. Hence the diagnosis was restricted to CKD from HIV (and not HIVAN as the diagnosis needs histological confirmation). Apart from HIVAN, other glomerular lesions in HIV infection include HIV-immune complex disease (mesangial proliferative, membranoproliferative [types I and II], lupus-like, exudative-proliferative, crescentic, IgA, membranous), varioug glomerulonephropathies (minimal change disease, membranous nephropathy, immunotactoid nephropathy, amyloidosis), HIV-thrombotic thrombocytopaenic purpura/ haemolytic uraemic syndrome. Tubulo-interstitial disease include acute kidney injury, proximal tubular injury, chronic tubular injury, crystal nephropathy and interstitial nephritis.

Treatment of the renal disease in the index patient included haemodialysis because of uraemia, changing the ART regimen due to presence of proximal tubulopathy, use of ACE-I for antiproteinuric effect, diuretics to control edema and haematinics for treatment of anaemia. Observational studies and data from uncontrolled or retrospective studies[17-19]and from an RCT[20] suggest that HAART (defined as combination therapy with three or more drugs) is beneficial in both preservation and improvement of kidney function in patients with HIVAN. Treatment with HAART is effective in HIVAN, but may not effective in other GN associated with HIV infection.[21] Use of HAART was beneficial in this patient as evidenced by improvement in general well being of the patient, reduction in viral load and increase in CD4 count (see table 2). Nonrandomized studies in HIV-associated renal disease suggest benefit from corticosteroid, but because the efficacy appears to be modest and ofte short-lived, this is not considered standard therapy.[16]

Options for renal replacement therapy in patients with HIV infection include haemodialysis, peritoneal dialysis and kidney transplantation.[16] Strict use of universal precautions is advocated to prevent transmission in dialysis units. Concerns of staff and patients result in these patients been dialyzed in separate facilities in some institutions, although they do not need to be isolated from other patients.[16] Native arteriovenous fistulas are the preferred types of access because of better patency rates once established and lower complication rates. The nucleoside reverse transcriptase inhibitors are not tightly protein-bound and low to medium

molecular weight and therefore can be easily removed by dialysis. With the exception of abacavir, the NRTIs should generally be administered after dialysis.[11]

Human immunodeficiency virus has been known to survive in peritoneal effluents at room temperature for up to 7 days and in peritoneal exchange tubings for up to 48 hours.[22] Dialysate should therefore be handled as a contaminated body fluid. Patients on peritoneal dialysis should be instructed to pour dialysate into the home toilet and to dispose of dialysate bag and lines in conventional gabage. Sodium hypochlorite (50% solution) and household bleach (10% solution) is effective at killing HIV in dialysate. Kidney transplantation has been performed with success in HIV-infected patients and patients survival is similar to those of HIV-uninfected transplant recipients and there have been no increase in the prevalence of opportunistic infections.[23] In areas with high endemic rates of HIV infection, it has been proposed that HIV-infected cadaveric donor organs may be transplanted into HIV-infected recipient with ESRD.[24]

LIMITATION: Absence of histopathologic diagnosis in this case is a recognized limitation of this study.

Table 1: Result of investigations done for this index patient.

Variable	Result	Reference values
Urinalysis-Protein	3+	Nil to trace
Blood	1+	Nil
Glucose	2+	Nil
Urea	131	15-50
Creatinine	6.7	0.5-1.3
eGFR (mL/min/1.73m^2)	11	90-120
Potassium	6.0	3.5-5.5
Sodium	142	130-145
Bicarbonate	15	20-28
Random blood sugar (mg/dl)	98	60-200
White blood cells (cells/µl)	14x10^3	4-11x10^3
Haemoglobin (g/dl)	6.5	10.5-13.5

Platelets (cells/µl)	230	150-400
Mean cell volume (pg)	82	80-100
Mean cell haemoglobin (pg/l)	29	27-34
Urine protein: creatinine ratio (mg/g)	2,450	20-200
Fractional tubular resorption of phosphate	0.71	>0.82
CD4 count (copies/ml)	97	>500
Serum calcium	6.3	8.6-10.2
Serum phosphate	6.0	2.5-4.8

Table 2. Serial values of some parameters during follow up at the nephrology clinic

	Creatinine (mg/dl)	**Hb (g/dl)**	**PCR (mg/g)**	**CD4 count (cells/µl)**	**Fractional Phosphate reabsorption**	**Viral load (copies/ml)**
At discharge	2.1	9	1,610			
3rd week	1.7	9.5	481	201	0.89	
12th week	1.4	10.5	289	241	0.91	302

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