CASE REPORT

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Late onset of HIVAN in a young female – a case report

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Abstract

Introduction: Human Immunodeficiency Virus associated Nephropathy (HIVAN) is a relatively frequent pathology among HIV patients, especially in black patients. Among about 800 HIV-infected patients from the Western Romania cohort, mainly of subtype F, none were diagnosed documented with renal biopsy with HIV-associated nephropathy. Renal alterations etiology seems to be complex. Several renal abnormalities have been described among HIV-infected patients. *Patient, Methods and Results*: We discuss the case of a 24-year-old white Caucasian female HIV-infected in 1990 by horizontal transmission, in her first year of life. She was diagnosed as late-presenter stage C3 at the age of 10, when she was admitted in coma secondary to toxoplasmic encephalitis. The clinical evolution was favorable under antiretroviral treatment until 2003 when dyslipidemia and arterial hypertension appeared. The first clinical manifestations of nephropathy were detected in 2006, with altered values of creatinine clearance. A 7-year follow-up of renal impairment shows a descending trend of creatinine clearance values. We analyzed the repeated ultrasound findings and renal biopsy was performed in 2013 revealing aspects of HIVAN. It has become obvious that HIVAN is caused by direct effects of HIV-1 virus over kidney structure and also that within the renal cells, viral replication is still permitted. In our case, the viral load peaked in 2011 at the same time the renal function significantly deteriorated. Her lifestyle changes must be taken under consideration – in the last year she has been under a low protein regimen. Compliance to antiretroviral treatment improves survival rate with a delayed deterioration of renal function to end-stage renal disease. *Conclusions*: Renal biopsy remains the most important feature in order to diagnose HIVAN. Suspicion of HIVAN diagnosis should be taken under consideration in the presence of constant proteinuria as well as decreased creatinine clearance levels.

Keywords: AIDS, HIVAN, HAART, renal biopsy.

Introduction

Human Immunodeficiency Virus associated nephropathy (HIVAN) is a relatively frequent pathology among HIV patients, especially in African countries. The overall HIVAN prevalence in the general population is 6.9% with a specific black HIV patients prevalence of 12% as the overwhelming majority (93%) of HIVAN autopsied patients were black [1, 2]. This entity was recently added to the 1988–1990 Romanian HIV-infected cohort.

Amongst about 800 HIV-infected patients from the Western Romania cohort, mainly of subtype F, none were diagnosed with HIV-associated nephropathy until 2013. Pioneering this added pathology, on a simple retrospective study, renal manifestations have been various: renal lithiasis, hematuria, proteinuria up to nephrotic syndrome and renal failure.

Similar to our findings, literature associates HIVAN by rapid loss of renal function (first described in 1984), proteinuria with a large range from minor proteinuria up to nephrotic proteinuria associated with the absence of edema due to protein loss [3–6], while blood pressure is normal or slightly increased.

Renal alterations etiology seems to be complex. Several renal abnormalities have been described among HIV-infected patients: HIV-related immune complex disease, nephropathy secondary to antiretroviral therapy (ART) or antibiotics, thrombotic microangiopathy or renal manifestations secondary to co-morbidities (diabetes mellitus, hypertension) [3, 5]. Renal biopsy is definitely the most accurate investigation in order to diagnose a patient with HIVAN. The most consisting finding on renal biopsy is a particular form of focal and segmental glomerulosclerosis with capillary collapse, but also other lesions such as cystic tubular dilatation, interstitial edema, cellular infiltrates and dilated tubules filled with pale-staining amorphous casts could be found [7]. These characteristic changes appear because of DNA and mRNA of HIV-1 incorporation into the renal parenchymal cells [8].

Antiretroviral therapy is proven to slow the progression of the renal disease towards end stage renal disease (ESRD) and also to increase the survival rate of patients [8]. And even if Highly Active Antiretroviral Therapy (HAART) improved survival rates in HIV-associated nephropathy, some of the antiretroviral regimens have been related to nephrotoxicity with crystal-induced obstruction after some protease-inhibitors use, mainly Indinavir and Atazanavir and proximal tubule damage related to the nucleotide analog reverse transcriptase inhibitor Tenofovir. Finally, specific HAART induce metabolic complications and might increase the risk of vascular chronic kidney disease in patients on therapy. However, given the benefits of HAART, fear of nephrotoxic effects is never a valid reason to withhold antiretroviral therapy [9–11], treatment switch is always an option, Tenofovir induced lesions are reversible if treatment is replaced in time, the same with Indinavir induced lesions. That is the reason monitoring patients is very important. Besides HAART, other potential beneficial

treatment options for HIV-associated nephropathy include angiotensin-converting-enzyme inhibitors, corticosteroids, dialysis, and renal transplant [12].

Patient, Methods and Results

We report the case of a 24-year-old white Caucasian female HIV infected in 1990 with horizontal HIV transmission, in her first year of life. She was diagnosed with HIV infection, as late-presenter and staged C3 at the age of 10 due to toxoplasmic encephalitis. Immune status at diagnosis was extremely low with a CD4 lymphocytes T-count of 6 cells/mm^3; at that time, viral load could not be performed. She immediately started treatment with one non-nucleoside reverse transcriptase inhibitor (NNRTI) and one protease inhibitor (PI) (Efavirenz and Indinavir) along with anti-toxoplasmic and supportive treatment. Encephalitis was resolved with sequel, consisting of central left disabling hemiparesis and recurrent seizures (now, under medication control). The clinical evolution was favorable until 2003 when dyslipidemia and arterial hypertension (AHT) were associated. She presented episodic candidiasis without any other clinical progression of HIV infection.

HAART side effects including dyslipidemia and arterial hypertension have been documented starting from 2005. Dyslipidemia was presented in laboratory findings with increased levels of cholesterol and triglycerides (Figure 1), but also clinical lypodystrophy was mentioned. The improvement in lipid levels was obtained by lipid-lowering therapy with Pravastatin and Ezetrol but she did not return within normal cholesterol values.

The first clinical manifestations of nephropathy were detected in 2006, at the age of 15 (Figure 2) with altered values of creatinine clearance (using for glomerular filtration rate the MDRD equation – 61 mL/min.) and constant protein loss without edema. A 7-year follow-up of renal impairment shows a descending trend of creatinine clearance values in spite of supportive treatment. Constant proteinuria was probable due to glomerular alterations.

AHT was detected starting from 2006 with maximum value of 160/105 mmHg, undergoing unsteady treatment with diuretics and starting 2009 angiotensin-converting-enzyme inhibitor (ACE inhibitors) (Captopril) on a regular basis. The difficulty in the management of hypertension and lack of positive treatment results are reasoned because of renal etiology of hypertension. Cardiac findings were normal.

In February 2013, osteodensitometry (DEXA) revealed osteopenia in both femoral heads and lumbar spine tissue, also ascribed to destruction of renal tissue, interpreted as both renal and acquired immune deficiency syndrome (AIDS) osteodystrophy (Figure 3).

Immune reconstruction and CD4 evolution under HAART was on a positive trend until 2011, when due to immunological failure, treatment was changed, as detailed below. After this immunological fall in 2011, immune reconstruction was poor, CD4 level does not overrun the verge of 400 cells/mm^3 (Figure 4).

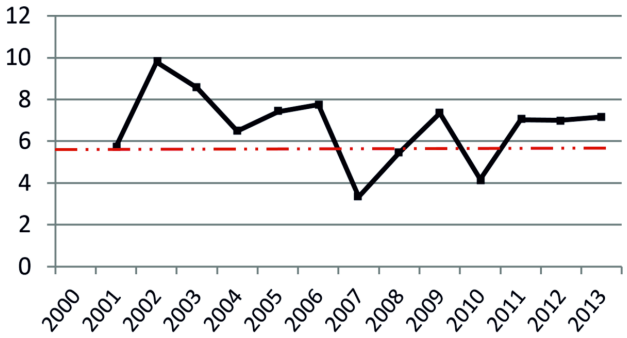

Figure 1 – ***Cholesterol levels [mmol/L] evolution in time. Beneath red dotted line, represent maximum cholesterol level admitted in our laboratory.***

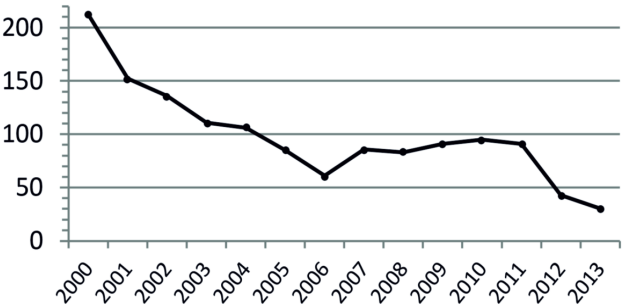

Figure 2 – ***Creatinine clearance levels [mL/min.]. First renal impairment (age of 15), see arrow.***

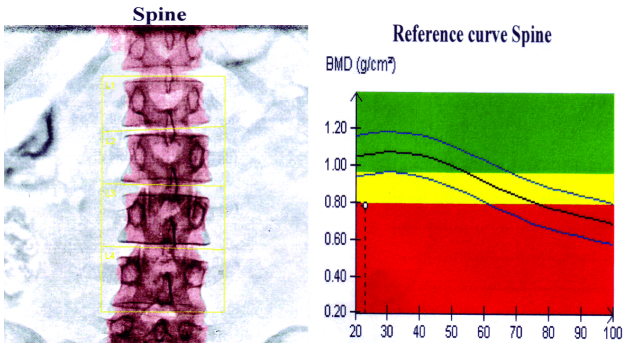

Figure 3 – ***Spine osteodensitometry showed osteoporosis.***

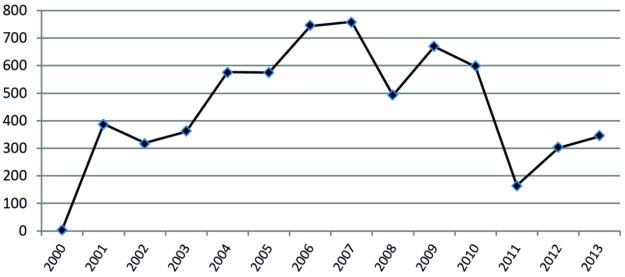

Figure 4 – ***CD4 cells/mm^3 correlated with immunological stages.***

In terms of HIV-RNA, we were able to maintain under detection limit, except one peak in 2011 simultaneously with the low level of CD4 count mentioned earlier, due to therapeutic failure (Figure 5).

Viral load detection limit was 400 copies/mL (2.6 $\log_{10}$) until 2008 and afterwards 50 copies/mL (1.7 $\log_{10}$) due to technique improvement.

Antiretroviral treatment consisted of using first treat-

ment regimen with Efavirenz and Indinavir for three years and afterwards Stavudine, Lamivudine and Nelfinavir (Figure 6). Under last treatment regimen, the patient experienced dyslipidemia, hypertension and also alterations of lipid metabolism on laboratory findings, therefore after 10 months the treatment was changed to Kivexa and boosted Saquinavir. Five years later, during favorable evolution on the same treatment, a high HIV-RNA was detected on routine analysis (HIV-RNA 98 036 copies/mL) together with a low CD4 cell count, interpreted as virological and immunological failure, leading to a new treatment plan (Combivir + boosted Prezista) followed by a poor immune reconstruction but with undetectable viral load. Continuous alteration of renal function (Figure 2) required careful clinic monitoring and treatment dose adjustments.

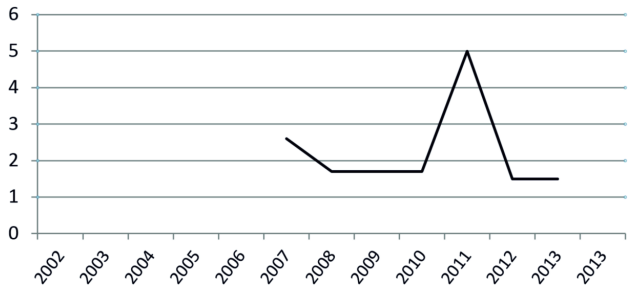

Figure 5 – ***Viral load (log_{10}) evolution.***

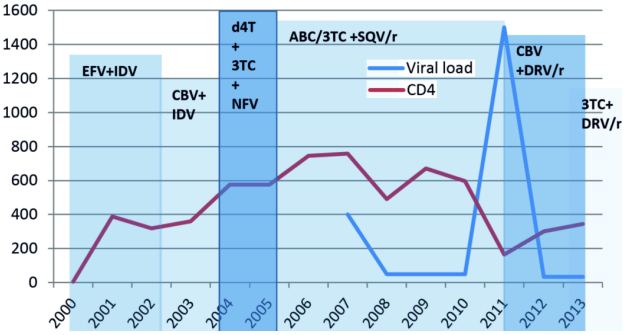

Figure 6 – ***CD4 and viral load evolution in time correlated with antiretroviral treatment. EFV: Efavirenz, IDV: Indinavir, CBV: Combivir, d4T: Stavudine, 3TC: Lamivudine, NFV: Nevirapine, ABC/3TC: Kivexa, SQV/r: Boosted Saquinavir, DRV/r: Boosted Darunavir.***

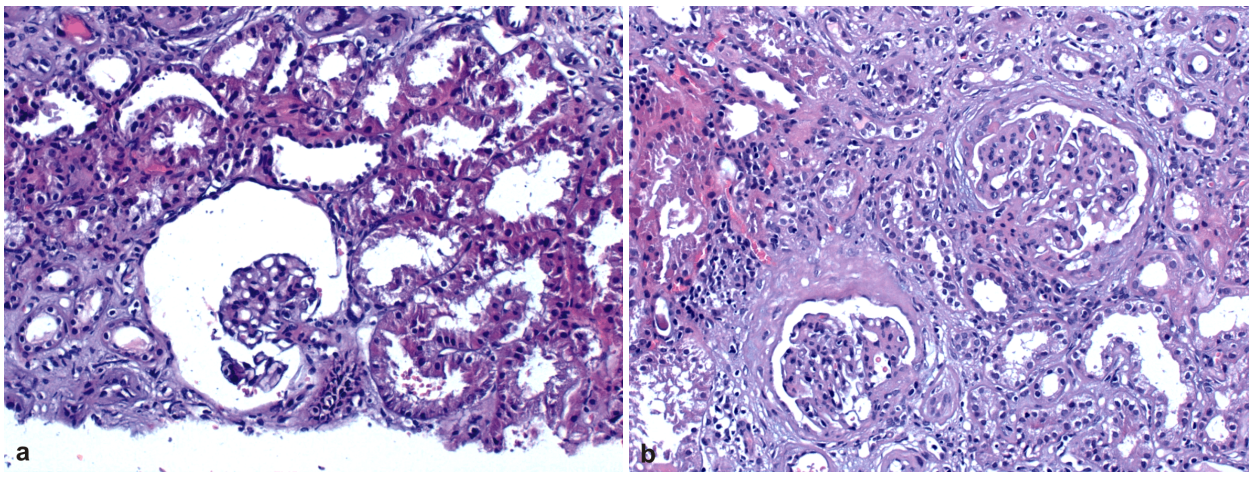

Figure 7 – ***(a and b) Renal parenchyma with sclerotic/atrophic glomeruli – some corpuscles with complete sclerosis and others with filtration space expanded, glomerular basal membrane thickened and wrinkled (duplicative aspect), increased mesangial matrix with diffuse sclerosis of the glomerular capillary and some with collapsed capillary. Hematoxylin–Eosin (HE) and PAS staining, 200×.***

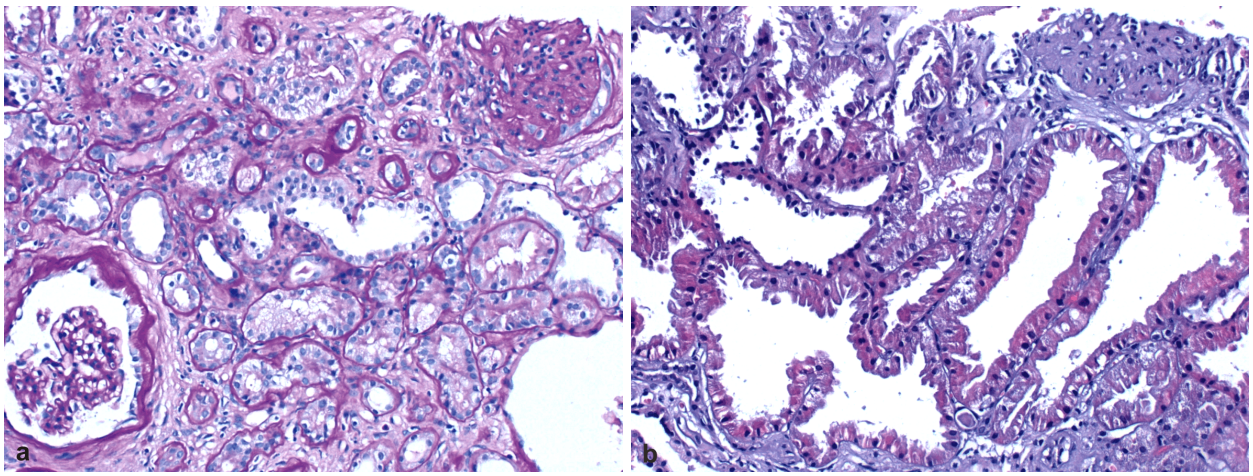

Figure 8 – ***(a and b) Renal tubules with thickened basal membrane, global fibrosis, renal interstitial tissue with abundant lymphoplasmocytic inflammatory infiltrate with spot disposal. Arteriolar hyalinosis, dilated tubules, epithelial and granular tubular dystrophy. HE and PAS staining, 100×.***

In order to assess the case as HIV-associated nephropathy, we retrospectively analyzed ultrasound findings. Ultrasound imaging showed moderate enlarged kidneys, increased cortical echogenicity with a poor corticomedullary differentiation on both kidneys.

Renal biopsy, performed in 2013, revealed renal parenchyma with sclerotic/atrophic glomeruli – some corpuscles with complete sclerosis and others with filtration space expanded, glomerular basal membrane thickened and wrinkled (duplicative aspect), increased mesangial matrix with diffuse sclerosis of the glomerular capillary and some with collapsed capillary (Figure 7). Renal tubules with thickened basal membrane, global fibrosis, and renal interstitial tissue with abundant lymphoplasmocytic inflammatory infiltrate with spot disposal (Figure 8). The morphological findings on renal biopsy suggest a particular form of focal and segmental glomerulosclerosis evocative for HIV-associated nephropathy alterations.

Morphological findings correlate with slow progressive renal impairment and constant proteinuria due to both glomerular and tubular alterations. The slow gradual progression rate indicates a chronic degenerative process aiming to severe chronic kidney disease. Good treatment adherence determines slower progression of renal alterations, which leads to longer pre-dialysis stage.

Discussion

HIVAN is the major cause of chronic kidney disease in HIV patients, with a high prevalence in the black race [13, 14]. Early recognition of the disease is crucial for its evolution as despite HAART most patients reach end-stage-renal-disease (ESDR) [14]. It is notable that we found only very few cases with renal impairment in our 800 patient cohort, with yet only one proven HIVAN diagnosis. The vast majority of our patients are Caucasians, so race disparities may play a role in the lower frequency of this diagnosis. Gender disparities in HIV/AIDS progression are clearly documented and less than one tenth to one third of white HIVAN patients were females, according to previous studies [12, 15–17].

Having moderate to massive proteinuria, patients seem to develop chronic kidney disease (CKD) in a short period of time, apart from other clinical manifestations pointing to survival rate less than 36% at two years [16, 18]. Symptoms are non-specific but may include fatigue, fever, anorexia and pruritus. Although 40–75% of patients have nephrotic range proteinuria at presentation and many have signs of full nephrotic syndrome with hypoalbuminemia; peripheral edema is uncommon [13, 19]. The characteristic findings of HIVAN are: black patient with somehow late-stage HIV infection presenting proteinuria, high serum creatinine level and enlarged echogenic kidneys as ultrasound findings [19–23]. Renal biopsy remains the ultimate assay for diagnosis. The entity is characterized by histological findings, which are consisting with a collapsing form of focal glomerulosclesclerosis – collapsed glomerular tufts, with thickening and wrinkling of the glomerular basement membrane, tubular atrophy and dilatation containing protein-rich casts [18, 22–24]. Other studies describe the entity as a mesangial proliferative glomerulonephritis, found on most cases of 26 HIV-infected Asian patients [21].

Response to HAART regarding renal lesions could be seen using seriated renal biopsies on naïve HIV-infected patients with renal impairment followed by a second/third renal biopsy after 25 months of ART. Comparison showed time-dependent but incomplete resolution of immune complex deposits and persistence of the chronic active interstitial nephritis [24, 25]. Better improvement was seen in early stages of HIVAN after HAART [25]. In clinical response to ART, improvement was seen by viral suppression and rises in median CD4 counts [25]. The true challenge remains within the pluri-medicated HIV patient with HIVAN histological findings.

The term HIVAN is reserved for the typical histopathological form of focal and segmental glomerulosclerosis (FSGS) found both in humans and the murine model with glomerular collapse and podocyte hyperplasia. The tubulointerstitial damage and glomerular collapse can also be seen in non-HIV primary collapsing glomerulonephritis, raising the question of common mechanisms to HIV and other non-identified viral agents related in the pathogenesis of disease [13, 26].

Studies performed on mice revealed that most probably HIVAN's finest alterations developed in the early time of seroconversion, long before AIDS symptoms became clinically manifest and evolution of disease is independent of HIV viral load in terms of renal impairment [2, 12, 14]. It has become clear that HIVAN is caused by direct effects of HIV-1 virus over kidney structure and also that within the renal cells, viral replication is still permitted [12, 18]. In our case, the viral load peaked in 2011 at the same time the renal function significantly deteriorated.

We try to explain the fact that 24-year-old white female undergoing HAART, diagnosed with decline of renal function, and now diagnosed with HIVAN lived for seven years in a good condition. The question still remains whether she lives as an exception to an unwritten rule of bad outcomes, or because of racial and gender disparity combined with good treatment and lifestyle changes. This would be the reason why renal disease appears to be under control [13, 16].

Lifestyle changes must be taken under consideration – in the last year she has been under a low protein regimen, she is currently unemployed and with a moderate degradation of self-care capacity (walking and dressing difficulties secondary to hemiparesis, mental impairment due to HIV encephalopathy), in need of social assistance, but with a positive and optimistic attitude.

Conclusions

Adherence to antiretroviral treatment improves survival rate with a delayed deterioration of renal function to end-stage renal disease. Early HIVAN suspicion in presence of proteinuria and early diagnosis with renal biopsy may improve the evolution ratings in presence of antiretroviral treatment. Our case undeniably has a great compliance to treatment, therefore the rapid alteration of the creatinine clearance levels and degradation of the kidney function expected in classic HIVAN is not yet apparent in this case. We did not discover other associated pathologies

that can determine renal function loss, knowing that HIVAN changes on biopsy can be found in other pathology. Renal biopsy remains the most important feature in order to diagnose HIV-associated nephropathy. Suspicion of HIVAN diagnosis should be taken under consideration in the presence of constant proteinuria as well as decreased creatinine clearance levels in HIV patients.

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