Amyloidosis related to HIV – An unusual cause of nephrotic syndrome in HIV patients

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ABSTRACT

Human immunodeficiency virus infection is a multisystemic disease which causes kidney disease in a variable proportion of infected patients. AA amyloidosis, in turn, is an unusual complication related to HIV infection and also an infrequent cause of kidney disease; in this setting AA amyloidosis usually results from chronic skin infections related to intravenous use of recreational drugs. We report the case of a 43-year-old woman, native of the Ivory Coast, with active HIV 1 infection diagnosed 11 years ago, currently in the Centers for Disease Control and Prevention’s stage C3, out of antiretroviral therapy for non-adherence and with persistent positive viral load, admitted to the nephrology department for nephrotic syndrome. The patient denied any other relevant clinical history, including chronic or recurrent inflammatory or infectious disease or use or abuse of recreational drugs. Urine sediment and renal function were both normal as was renal ultrasound. Other opportunistic infections were excluded. The renal biopsy revealed deposition of amorphous substance, Congo red positive, in the vascular walls and a positive immunofluorescence for serum amyloid A, confirming the diagnosis of renal amyloidosis. The patient was started on antiretroviral and symptomatic therapy, with clinical improvement. The clinical diagnosis of renal amyloidosis secondary to HIV can be challenging, as it requires the exclusion of other possible aetiologies, but should be considered in the differential diagnosis of renal disease in HIV patients. This case illustrates the importance of the renal biopsy in such cases in which the diagnosis can be improperly set up if based only on clinical data.

Key-Words: AA amyloidosis; antiretroviral therapy; human immunodeficiency virus infection; nephrotic syndrome; renal biopsy.

INTRODUCTION

Human immunodeficiency virus infection (HIV)/acquired immune deficiency syndrome (AIDS) is a multisystemic disease which has become a global pandemic¹. With prolonged survival and aging of the HIV-infected population in the era of antiretroviral therapy, a growing number of diseases affecting different organ systems in the general population are becoming manifest in these patients², as is the case of kidney disease related to HIV infection¹. Patients with HIV are at risk of both acute kidney injury (AKI) and chronic kidney disease (CKD), secondary to nephrotoxic medication, HIV-associated nephropathy (HIVAN) and other glomerulopathies². In addition, HIV-positive patients may be at increased risk of progressive kidney disease related to hepatitis B or C virus co-infection, and comorbid or treatment-related diabetes and hypertension². Renal disease in HIV-infected patients was first described by Rao et al³ in 1984, as a focal and segmental glomerulonephritis subsequently termed HIVAN, and although this is usually the most common
CASE REPORT

We report the case of a 43-year-old melanodermic female patient, native of the Ivory Coast, resident in Portugal for several years, who was referred to the Department of Nephrology after a 10-day history of swelling of the lower extremities and hypertension.

The patient had active HIV-1 infection diagnosed 11 years ago and was in CDC (centers for disease control and prevention) C3 stage. The antiretroviral therapy had been precociously interrupted for non-adherence and the patient maintained positive viral load over the time. Six months before the current episode, she was started on emtricitabin, tenofovir, lopinavir and ritonavir, again with poor compliance. The last measurement of viral load result was 600 copies/ml (15 days before) and the CD4+ T cells were 243/µl (2 months before). Furthermore, there was a history of cholelithiasis, uterine leiomyoma and depressive disorder for which she had been recently medicated with amitriptyline 25mg daily. The patient denied any further relevant medical history, in particularly hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, chronic or recurrent inflammatory or infectious disease, such as mycobacterial infection, pneumocystis, toxoplasmosis, CMV infection or other related to HIV infection, or neoplasms. She also denied the use of intravenous drugs and no familial history of AA amyloidosis was known.

Upon admission, clinical examination showed pronounced lower limb oedema and a blood pressure of 160/80 mmHg. No history of fever, haematuria or other urine abnormalities was disclosed, and no respiratory or gastrointestinal symptoms were present.

The laboratory studies revealed microcytic/hyPOCHROMIC anaemia (9.9g/dl) associated with iron deficiency, hypoalbuminaemia (2.8g/dl), hypercholesterolaemia (268mg/dl) and a nephrotic proteinuria of 13g/24h, with bland urine sediment, consistent with the diagnosis of nephrotic syndrome. The leukogram and platelets were normal as were serum creatinine urea and ionogram. Blood tests were also negative for autoimmune diseases, monoclonal gammopathies, HCV, HBV, syphilis infection or other opportunistic infections. The renal ultrasound showed normal-sized kidneys, a mild renal parenchyma hyper-echogenicity. In order to clarify the aetiology of the nephrotic syndrome, the patient underwent renal biopsy, which showed deposition of amorphous substance in all the 7 glomerulus presented in the biopsy and in the vascular walls (Figure 1), with a positive Congo red staining (Figures 1 and 2), tubular atrophy (35%) and interstitial fibrosis (35%). The immunofluorescence was positive for amyloid A and negative for kappa and lambda chains (Figure 4). The screening of other organs for amyloid deposition detected a mild hepatosplenomegaly and was otherwise negative, including the transthoracic echocardiography.

At the time of diagnosis, the patient was started on diuretic and anti-proteinuric therapy, and a significant clinical improvement followed. The antiretroviral...
therapy was changed with tenofovir eviction, in order to prevent further renal lesion. The patient evolved with regression of proteinuria (~0.5g/24h) and maintains a normal renal function at the 6 month follow up, under antiretroviral therapy and low dose angiotensin II receptor antagonist.

**DISCUSSION**

As the prevalence and survival of HIV is increasing, the spectrum of renal disorders in HIV patients is also changing and all varieties of glomerular and tubulointerstitial disorders can be found on histology. AA amyloidosis is an uncommon cause of renal disease and nephrotic syndrome in HIV-positive patients and usually occurs as a complication of chronic inflammatory or infectious disease. In the past, it was reported in intravenous or subcutaneous drug abusers, some of whom were HIV-positive.

Two studies from Europe reported an increased prevalence of renal AA amyloidosis in patients with IVDU. However, only a few cases have been recorded in the literature of HIV-infected patients with AA...
amyloidosis who have no history of drug consumption. In 1992 Cozzi et al11 described AA amyloidosis in association with HIV infection in a 38-year-old patient with HIV infection and haemophilia, with an history of multiple transfusions and a right hip inflammatory process related to an infected prosthesis (without evidence of osteomyelitis). In this case, the underlying disease was uncertain and the authors suggested that AA amyloidosis should be considered in the differential diagnosis of nephrotic syndrome in patients with AIDS. Jatem et al7 reported the case of a patient with an HIV infection who was a chronic user of intravenous drugs and developed acute renal failure and nephrotic syndrome due to secondary AA amyloidosis. They did not identify any condition that could explain the presence of the secondary AA amyloidosis, but given the long evolution of the HIV infection and drug abuse, it would be impossible to discern the cause of the AA amyloidosis. Navarro et al13 describes a case of non-oliguric acute renal failure with nephrotic syndrome in a Caucasian patient with both HIV and HCV infections, in whom the biopsy showed AA amyloidosis. This was a case of AA amyloidosis not preceded by recurrent infections, in which recovery of the renal function and resolution of the nephrotic syndrome were objectively demonstrated after antiretroviral therapy, similarly to our case.

The clinical case we hereby describe is an HIV-positive patient who presented with nephrotic syndrome but without renal failure. Given the medical history, the differential diagnosis included HIVAN, non-HIVAN focal and segmental glomerulosclerosis and other glomerulopathies such as AA amyloidosis, which a renal biopsy subsequently confirmed. However, no history of drug abuse, chronic infection or other disorder usually associated with reactive AA amyloidosis was found, leading to the conclusion that the AA amyloidosis was secondary to the long-term uncontrolled HIV infection itself. Observational studies have suggested that antiretroviral medications and angiotensin-converting enzyme inhibitors have beneficial effects, slowing the progression of renal disease in HIVAN patients. Still, little is known about the effect of these therapies on other renal lesions, namely on AA amyloidosis.5 In the present case, the treatment has been effective, at least in the short term.

In HIV patients with renal disease, the CD4 cell count at presentation seems to be associated with progression to ESRD, namely in HIVAN. The question remains whether the same occurs in AA amyloidosis secondary to HIV, but it seems likely that the immunologic status may be related to a more aggressive renal disease and a faster progression to end stages.5 Szczech et al16 observed that an absolute CD4 cell count of ≤200 cells/mL, a detectable HIV RNA level, increasing systolic blood pressure, increasing creatinine and decreasing albumin are predictors of progression of renal disease among women with HIV-related renal diseases and proteinuria, meaning that this markers of viral replication and immune status may have an impact on the mechanism of the progression of nephropathy. In our patient, some of these predictors were present and she also had a heavy proteinuria, which probably justify a tighter follow-up and monitoring of renal function.

In conclusion, HIV-related renal dysfunction is an important entity with quite variable aetiology and AA amyloidosis should be considered in the differential diagnosis, particularly in patients with nephrotic syndrome.11 The clinical diagnosis of AA amyloidosis secondary to HIV infection itself as the cause for renal disease can be challenging, as it requires the exclusion of other more frequent causes, such as HIVAN. Therefore, histology is crucial because the clinical diagnosis, based on degree of proteinuria, CD4 count or viral load, may not predict the pathological diagnosis in HIV-positive patients.6,17 More studies are needed to reach a better understanding of the prognosis and more appropriated treatment.

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References

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