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
histologic renal lesion in these patients, renal biopsy series have found a broad spectrum of HIV-related kidney disease\(^6\), such as membranoproliferative glomerulonephritis, minimal change disease, membranous glomerulopathy, immunocomplex glomerulonephritis, IgA nephropathy and AA amyloidosis, which together make up as much as one-third of cases\(^5\). Our understanding of the epidemiology and clinical course of these other HIV-related renal diseases remains limited\(^5\).

AA amyloidosis is an uncommon cause of renal disease in HIV patients\(^6\),\(^7\). It is a disorder of the protein metabolism that can complicate a number of chronic inflammatory and infectious diseases\(^8\) characterized by ongoing or recurring inflammation that results in the production of serum amyloid A, an acute phase reactant which can form amyloid deposits\(^9\). Usually present as a nephrotic syndrome, with progressive loss of renal function\(^5\), AA amyloidosis can be associated with a heterogeneous group of disorders, with autoimmune diseases the most common causes of AA amyloidosis in developed countries, whereas untreated chronic infections are the predominant cause in countries with limited medical resources\(^10\). The aetiology mechanisms of AA amyloidosis in the context of HIV infections is not well established\(^11\); AA amyloidosis in this setting usually occurs as a result of chronic infections, particularly skin infections related to intravenous use of recreational drugs\(^7\). Renal disease related to intravenous drug use (IVDU) has been reported since the 1970s, in that period mostly in the context of heroin-associated nephropathy\(^10\). Despite the yet unclear nature of the relationship between AA amyloidosis and HIV, it has been observed that serum amyloid A protein (SAA) levels are high in patients with chronic infections\(^12\), such as non-controlled HIV infection, which would, in theory, predispose the patient to the development of AA amyloidosis. The increased frequency of AA amyloidosis in HIV-infected patients has been hypothesized as being related to the progressively higher life expectancy of these patients and the observed increased secretion of amyloid\(^13\).

**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 autoimmunity 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 immuno-fluorescence 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\(^1\). AA amyloidosis is an uncommon cause of renal disease and nephrotic syndrome in HIV-positive patients (6, 7) 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\(^6\).

Two studies from Europe reported an increased prevalence of renal AA amyloidosis in patients with IVDU\(^{14,15}\). However, only a few cases have been recorded in the literature of HIV-infected patients with AA...
showed AA amyloidosis. This was a case of AA amyloidosis associated with both HIV and HCV infections, in whom the biopsy initially showed chronic heavy proteinuria due to amyloidosis in an HIV-infected patient. Am J Med Sci 2006; 332(6): 428-434. 5. Szczech IA. Renal diseases associated with human immunodeficiency virus infection: epidemiology, clinical course, and management. Clin Infect Dis 2001; 33: 115-119. 6. Chan-Tack KM, Ahuja N, Weisman EJ et al. Acute renal failure in HIV-infected patients. Am J Med Sci 2006; 332(6): 364-367. 7. Jatem E, Loureiro J, Curran A. Secondary amyloidosis in a HIV patient. Nefrologia 2011; 31(6): 747-764. 8. Causes and diagnosis of secondary (AA) amyloidosis and relation to rheumatic diseases. Available at https://www.uptodate.com. Accessed January 16, 2017. 9. Overview of amyloidosis. Available at https://www.uptodate.com. Accessed January 16, 2017. 10. Jung O, Hzaack HS, Buettner M et al. Renal AA-amyloidosis in intravenous drug users—a faster progression to end stages? 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 aetiology1 and AA amyloidosis should be considered in the differential diagnosis, particularly in patients with nephrotic syndrome11. 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 patients6,17. 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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