Teaching Point
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Discontinuation of antiretroviral therapy causing progression to end-stage renal disease in HIV patient diagnosed with immune complex ‘lupus-like’ glomerulonephritis

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Abstract
Immune complex ‘lupus-like glomerulonephritis’ is a type of renal injury seen infrequently in human immunodeficiency virus (HIV) patients and very little is known about the clinical course and treatment. Treatment options are limited but antiretroviral therapy and steroids have been tried with limited success. We report a case of a 21-year-old HIV-positive African American male with lupus-like glomerulonephritis who progressed to end-stage renal disease upon discontinuation of highly active antiretroviral therapy. This case illustrates the importance of antiretroviral therapy as an important treatment modality for immune complex lupus-like glomerulonephritis in HIV patients.

Keywords: antiretroviral therapy; end-stage renal disease; HIV; lupus-like glomerulonephritis

Introduction
The most common renal lesions associated with the human immunodeficiency virus (HIV) are collapsing focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy. Lupus-like glomerulonephritis is a type of immune complex-induced renal injury seen rarely in HIV patients which is characterized by histological, immunological and ultrastructural features of lupus nephritis but occurs in patients who do not have evidence of systemic lupus erythematosus (SLE).

There is very limited data regarding its clinical course, outcome and treatment. We present a case of an HIV patient found to have repeated ‘lupus-like’ glomerulonephritis on renal biopsy done 4 years apart with progression to end-stage renal disease following withdrawal from antiretroviral therapy.

Case report
A 21-year-old African American male presented to our hospital in November 2010 with a 1-week history of hematuria, bilateral pedal edema, flank pain and vomiting. He also noted a weight gain of 9 kg over the past 5 months. About 2 months prior to admission, the patient had stopped his highly active antiretroviral therapy (HAART) and lisinopril citing insurance reasons.

Physical examination was significant for periorbital edema, 2+ pitting peripheral edema, bilateral costovertebral angle tenderness and palpable lymphadenopathy. Initial laboratory workup revealed a serum creatinine of 875.16 μmol/L (baseline creatinine was 132.6 μmol/L); estimated glomerular filtration rate (eGFR) 6.7 mL/min/1.73m² (0.11 mL/s/1.73m²) calculated using the four-variable Modification of Diet in Renal Disease Study equation. Urine analysis showed 3+ protein, 2+ blood, 6–10 red blood cell and was negative for esterase and nitrite. Serum albumin was 2.1 g/dL, low-density lipoprotein was 176 mg/dL and 24-h urinary protein was 22 g. Complement levels were within normal limits.

Serological workup for anti-streptolysin O antibody, anti-DNase B, double-stranded DNA and anti-nuclear antibodies (ANA) was negative. CD4 count was 420 cells/μL and HIV viral load was 79 998 copies/mL. Renal ultrasonography showed normal sized kidneys with no mass or obstruction.

The following differential diagnoses were considered: (i) HIV nephropathy, (ii) rapidly progressive glomerulonephritis, (iii) acute tubular injury due to nephrotoxic HIV medications or volume depletion and (iv) lupus-like glomerulonephritis. The patient underwent percutaneous kidney biopsy, which was diagnostic of lupus-like proliferative glomerulonephritis (Figure 1).

HAART was restarted and he was given Lasix and intravenous Solumedrol. The edema became refractory to diuretics and serum creatinine trended to 1095.16 μmol/L eGFR.
5.2 mL/min/1.73m² (0.086 mL/s/1.73m²) at which time hemodialysis was initiated.

Renal biopsy findings

In 2006, the kidney biopsy contained 12 glomeruli of which 2 of the viable showed FSGS. Four of the glomeruli were globally sclerosed and obsolescent (30%). The viable glomeruli were normal in size and showed minimal mesangial hypercellularity. There was absence of glomerulus basement membrane thickening, extra capillary crescentric cellular proliferation and infiltrating polymorphonuclear cells. The interstitium showed mild patchy chronic inflammation. There was mild patchy tubular atrophy and dilation with no evidence of cystic dilation. Many tubules showed hyper-eosinophilia of the tubular epithelial cytoplasm with focal resolution of the cytoplasmic membrane and drop out of the tubular epithelial nuclei, which was consistent with acute tubular necrosis. Immunofluorescence microscopy findings showed strong granular mesangial glomerular staining with IgG (4+) and C3 (3+). Focal mesangial IgA staining (2+) and very weak (0-1+) IgM mesangial staining was also present. It was negative with fibrinogen.

In 2010, the kidney biopsy contained seven glomeruli (Figure 1B), of which six glomeruli were globally sclerosed (86%). There was moderate tubular atrophy and interstitial fibrosis. The interstitium showed severe mixed diffuse inflammatory infiltrate composed of lymphocytes, plasma cells, neutrophils and few eosinophils. Tubules had patchy moderate cystic dilation with focal scalloped edges and contained tubular proteinaceous droplets (Figure 1C). Many tubules contained refractile eosinophilic protein granules, which was compatible with proteinuria. Few tubules showed sloughed epithelium and mitotic activity, which was consistent with acute tubular necrosis. Immunofluorescence microscopy findings showed diffuse global glomerular staining with IgG (3+) (Figure 1A) and segmental glomerular staining with IgM (1-2+). Focal tubular cytoplasmic droplets were positive with IgA (3+). It was negative with C3 or fibrinogen. Neither of the two biopsies had adequate glomerulus for electron microscopic examination.

Discussion

Lupus-like glomerulonephritis is a form of immune complex glomerulonephritis that has been rarely reported in HIV-infected patients. Renal lesions in HIV patients are diverse clinically and morphologically. Clinically, renal manifestations include acute renal failure, nephrotic syndrome, electrolyte and tubular function abnormalities and progressive chronic renal failure. Pathologically, renal lesions can be specific as seen in biopsies, or non-specific, as seen predominantly in autopsies. HIV/AIDS is associated with three types of glomerular involvement on renal biopsies.

HIV-associated nephropathy (collectively known as HIVAN) is the most common renal lesion affecting 60% of individuals and, histologically, is characterized by collapsing FSGS and related mesangiopathy. Ten to fifteen percent of patients are found to have immune complex-mediated glomerulonephritis. The most frequent of them are hepatitis C-associated membranoproliferative glomerulonephritis and IgA nephritis. The remaining have tubulointerstitial diseases which include acute tubular necrosis, interstitial nephritis, renal infections and renal neoplasms (lymphoma and Kaposi’s sarcoma) [1].

Lupus-like glomerulonephritis is defined as the presence of the ‘full house’ of glomerular immunoglobulin (IgG, IgA and IgM) and complement deposits (C3 and C1q) often with large subendothelial deposits (wire loops) on immunofluorescence microscopy in the absence of serological and clinical evidence of SLE. Our patient had features characteristic of both lupus-like glomerulonephritis nephritis and FSGS on renal biopsy.

There have been very few cases of lupus-like glomerulonephritis reported in the literature. Hass et al. described a case series in HIV patients in which 14 of 77 patients were
found to have lupus-like glomerulonephritis on renal biopsy. Three biopsies showed concurrent HIVAN and 12 showed moderate or severe chronic change [2]. On review of 73 renal biopsies in Northern Italy, 5 cases of lupus-like glomerulonephritis were reported [3]. Another study carried out in Northern Italy described three cases of lupus-like glomerulonephritis in 26 white Italian patients [4]. In the series of 136 consecutive renal biopsies conducted in HIV patients at Columbia Presbyterian Medical Center in New York City from 1983 to 1998, four patients were found to have lupus-like glomerulonephritis [1].

Lupus-like glomerulonephritis is not found to be associated more commonly with any one race. A multicentric clinicopathological study was conducted in 60 HIV patients in Paris hospitals, of which 4 black and 6 white patients were found to have lupus-like nephritis [5]. Our patient was, however, African American.

The data on etiology, clinical outcome and treatment in patients with lupus-like glomerulonephritis are limited and need more research. It is postulated that lupus-like glomerulonephritis is due to a combination of polyclonal B-cell activation and defect in immune complex clearance [6]. In the case series described by Haas et al., 10 of the 14 patients presented clinically with nephrotic syndrome with microscopic hematuria and 9 had serum creatinine >3 mg/dL. ANA was negative in 11 of the 14 patients. Ten patients developed end-stage renal disease within 1 year of biopsy [2]. Tabechian et al. described a case of a 42-year-old HIV Caucasian male who presented with nephrotic syndrome and progressive renal failure with WHO Class IV diffuse proliferative lupus nephritis on initial and subsequent renal biopsies. He had no clinical or serological evidence of SLE and had stable renal function on HAART. His renal function progressively declined to end-stage renal disease when he discontinued HAART. They concluded that lupus-like glomerulonephritis is markedly responsive to HAART [7]. However, the use of antiretroviral therapy was not associated with a slower progression to renal replacement therapy in HIV patients with renal disease other than HIVAN in a retrospective study [8]. One case of lupus-like glomerulonephritis was identified, which underwent clinical remission after receiving treatment with antiproteases for 6 months [9]. Mialou et al. [10] reported clinical improvement with steroids and antiretroviral therapy in a 12-year-old white HIV child with lupus nephritis. The response of lupus-like glomerulonephritis in HIV patients to HAART and steroids needs to be determined.

Our patient presented clinically with nephrotic syndrome, hematuria and acute renal failure following discontinuation of HAART therapy. Although he was restarted on HAART and received a course of steroids, he progressed to end-stage renal disease and became hemodialysis dependent. Based on our observations with this patient, we support the role of HAART as a treatment modality for HIV patients with biopsy-proven lupus-like glomerulonephritis.

Teaching points

1. Lupus-like glomerulonephritis is a rare type of renal lesion seen in HIV patients.
2. It is diagnosed by presence of the ‘full house’ of glomerular immunoglobulin (IgG, IgA and IgM) and complement deposits (C3 and C1q) on microscopy in the absence of clinical or serological features of lupus.
3. It has a variable clinical presentation and can present as acute renal failure, nephrotic syndrome, hematuria or end-stage renal disease.
4. Treatment is debatable but HAART has been shown to prevent progression of renal disease.

Conflict of interest statement. None declared.

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