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Recurrent HIV-Associated Immune Complex Glomerulonephritis With Lupus-like Features After Kidney Transplantation

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Abstract

A spectrum of kidney diseases besides classic human immunodeficiency virus (HIV)-associated nephropathy (HIVAN) exists in HIV-infected patients. Immune complex–mediated glomerulonephritis has emerged as a significant contributor to the burden of kidney disease in this population, particularly in patients of non-African descent. Lupus-like nephritis, a form of immune complex glomerulonephritis with histologic features identical to lupus nephritis in the absence of clinical or serologic markers of lupus, is well recognized as a cause of end-stage renal disease in HIV-infected patients. None of the HIV-associated kidney lesions, whether classic HIVAN or non-HIVAN, has been reported to recur in kidney transplants. We report here for the first time clinical and histologic recurrence of HIV-associated lupus-like nephritis after successful kidney transplantation, causing proteinuria, hematuria, and impaired kidney transplant function.

INDEX WORDS

Human immunodeficiency virus (HIV); kidney transplantation; recurrent disease; recurrent glomerulonephritis; lupus nephritis

Chronic kidney disease is highly prevalent[1] in human immunodeficiency virus (HIV)-infected patients and has a substantial impact on morbidity and mortality.[2,3] Immune complex–mediated glomerulonephritis (GN) is the more common lesion in non-African HIV-infected patients[4–7] and is only modestly less likely than classic HIV-associated nephropathy (HIVAN) to account for glomerular disease in patients of African descent.[8–10] Kidney transplantation has emerged as a treatment option for end-stage renal disease (ESRD) in HIV-infected individuals.[11] We describe for the first time the recurrence of a form of HIV-associated immune complex–mediated GN, namely lupus-like nephritis, in the kidney transplant.

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CASE REPORT

A 25-year-old white woman with AIDS received highly active antiretroviral therapy (HAART) with good clinical response: $CD4^+$ T-cell counts improved to 200–500 cells/μL and HIV RNA became undetectable in serum. She developed proteinuria, microscopic hematuria, and progressively decreasing kidney function 5 years later in the setting of repeated HAART interruption. Despite reinstitution of HAART and control of HIV replication, kidney function decreased and proteinuria worsened.

A percutaneous kidney biopsy performed 8 years after the initial diagnosis of HIV infection showed glomeruli with cellular crescents, mesangial widening, and mesangial and endocapillary hypercellularity (Fig 1A). “Full-house” positivity consisting of mesangial and peripheral staining for C1q (3+), C3 (3+), immunoglobulin G (IgG; 3+), IgM (1+), and IgA (1+) was observed on immunofluorescence microscopy. Electron microscopy confirmed the presence of granular electron-dense immune-type deposits within the mesangial and subendothelial compartments. A diagnosis of diffuse crescentic immune complex–mediated GN with features of lupus-like nephritis was made. The patient had no clinical manifestations of lupus, normal complement levels, and negative serologic test results for hepatitis B, hepatitis C, antinuclear antibody, and anti–double-stranded DNA antibody. She received corticosteroids and cyclophosphamide without an appreciable response and initiated hemodialysis therapy shortly afterward.

Four years later, the patient underwent living unrelated kidney transplantation with steroid and basiliximab induction and maintenance on tacrolimus, mycophenolate mofetil, and prednisone. Serum creatinine (SCr) level stabilized at 1.3 mg/dL (estimated glomerular filtration rate [eGFR], 46 mL/min/1.73 m^2 calculated using the isotope-dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease [MDRD] Study equation). She remained on HAART with undetectable viremia (HIV RNA <75 copies/mL).

Two years after transplantation, the patient was noted to have an SCr level of 1.6 mg/dL (eGFR, 36 mL/min/1.73 m^2), new-onset microscopic hematuria, and proteinuria (urine protein-creatinine ratio, 500 mg/g). A biopsy of the transplanted kidney showed well-preserved architecture with no apparent light microscopic glomerular changes (Fig 1B). Immunofluorescence microscopy showed near–full-house mesangial staining for C1q (3+), C3 (2+), IgG (1+), and IgM (2+; Fig 1C). Electron microscopy confirmed the presence of electron-dense immune-type mesangial and rare subepithelial deposits without substructure or other distinctive features; moderate focal visceral epithelial cell foot-process effacement also was seen (Fig 1D). Given the patient’s history of HIV infection and native kidney biopsy showing lupus-like nephritis, these findings are consistent with an early stage of recurrent lupus-like nephritis.

Results of serologic testing for lupus (including antinuclear antibody and complement) and viral hepatitis again were negative. No specific therapy was instituted. Kidney function has remained stable over 18 months with SCr level of 1.4–1.6 mg/dL (eGFR, 36–42 mL/min/1.73 m^2), persistent microscopic hematuria, and low-grade proteinuria (protein excretion <1 g/d).

DISCUSSION

Kidney pathology is highly prevalent[4,12] in patients with HIV/AIDS and the classic lesion of HIVAN is collapsing focal segmental glomerulosclerosis,[13] typically seen in African American men who present with the nephrotic syndrome, large echogenic kidneys, and rapid progression to ESRD. Landmark studies[14,15] have provided evidence for direct viral infection of glomerular and tubular epithelial cells as the cause of HIVAN. Both HAART and angiotensin-converting enzyme inhibitors slow the progression of HIVAN to ESRD.[16]

However, not all kidney disease in HIV-infected patients is HIVAN, and a spectrum of kidney diseases other than classic HIVAN repeatedly has been shown[3–10] to occur. A retrospective US multicenter study of 89 patients with HIV infection and kidney failure found that 52% of patients had a pathologic diagnosis other than HIVAN,[8] with immune complex–mediated GN accounting for 14.6% of kidney lesions. In Europe and Asia,[5–7] HIV-associated immune complex–mediated GN has been seen in 37%–76% of kidney biopsy specimens.

Most individuals with HIV-associated immune complex–mediated GN are white.[5,6,8] In patients of African ancestry, although less common than HIVAN, immune complex–mediated GN still confers a substantial burden of kidney disease.[8–10] Patients with immune complex–mediated GN often present with hypertension, decreased kidney function, modest proteinuria (protein excretion, 1,000–3,000 mg/d), and microscopic hematuria. In the US cohort,[8] patients with non-HIVAN diagnoses tended to have higher $CD4^+$ T-cell counts, coexistent viral hepatitides, and a relatively benign clinical course.

The pathogenesis of immune complex–mediated GN in HIV-infected patients is not well understood, and a direct causal link between HIV and the various glomerular lesions has not been shown. Polyclonal B-cell activation and hypergammaglobulinemia are frequent in HIV-infected patients. Immune complexes containing HIV antigens have been detected in the circulation and eluted from kidney tissue in HIV-infected patients with proliferative GN,[17] supporting a direct pathogenic role for HIV in the development of immune complex–mediated GN. Other possibilities include a secondary or aberrant response to coexistent viral hepatitides or intercurrent infection or a coincidental finding. Host genetic factors likely modulate the phenotypic expression of kidney disease, as indicated by the different racial predilections of kidney pathology[5–8] and the clustering of kidney disease in families of patients with HIV and ESRD.[18]

GN with lupus-like features, in the absence of clinical or serologic evidence of systemic lupus, has been well described in a small but significant proportion of HIV-infected patients with decreased kidney function, constituting 18%–45% of immune complex–mediated GN in different series.[6,19] Varied light microscopic histologic patterns, such as focal or diffuse proliferative glomerular changes with wire loop subendothelial deposits or membranous nephropathy without proliferative changes, were identified. Lupus-like features included a full-house immunofluorescence pattern of immunoglobulin (IgG, IgA, and IgM) and complement (C3 and C1q) deposits in glomeruli, and subendothelial, mesangial, and subepithelial immune complex deposits by electron microscopy.[6,19] Subepithelial immune

deposits with a peculiar ball-in-cup reaction pattern from the basement membrane have been described in HIV-related immune complex–mediated GN,[10] although this finding may not be specific.[20] Foot processes may be effaced and endothelial tubuloreticular inclusions may be seen in lupus-like immune complex–mediated GN. Interestingly, the preponderance of patients in these series[6,19] were of African descent, suggesting that lupus-like immune complex–mediated GN may not have a strong racial predilection. The exact pathogenesis of the lupus-like histology is unknown. It is possible that polyclonal B-cell activation is responsible, although this is unproved.

There are few studies of treatment in patients with HIV-associated immune complex–mediated GN. HAART did not affect the progression of non-HIVAN kidney disease in a US multicenter cohort,[8] although another study suggested benefit.[9] Treatment focused solely on decreasing the production of immune complexes through the suppression of viral replication may not be sufficient to modify disease progression, and modulation of the inflammatory response at the level of the kidney may be needed in addition. The long-term outcome of HIV-associated lupus-like nephritis is unclear. Kidney survival was poor in the largest reported series,[18] with 71% developing ESRD within a year of diagnosis and no discernible benefit seen from HAART or corticosteroids. However, >80% of the biopsies showed moderate to severe chronicity, which may have influenced the outcome.

The reported incidence of recurrent lupus nephritis posttransplantation is highly variable (0%–54%), depending on factors such as population characteristics, period of observation, performance of serial biopsies, and type of pathologic examination.[21,22] Recurrence usually is subclinical, histologically mild, and only rarely causes transplant loss. To our knowledge, recurrent HIV-associated lupus-like nephritis causing proteinuria, hematuria, and decreased transplant function post–kidney transplantation has not been reported previously. HIV-associated immune dysregulation and autoimmune phenomena, which are postulated to have a role in the development of immune complex–mediated GN, may persist posttransplantation and possibly contribute to recurrence even in the absence of active viral replication. The absence of proteinuria and/or hematuria in the living kidney donor and the development of these manifestations in the recipient 2 years posttransplantation argue against transplanted disease. Likewise, the occurrence of a de novo GN with coincidentally similar features to the original kidney disease is unlikely, but possible. Testing for antiphospholipid antibodies or cryoglobulins was not pursued because the biopsy findings were not suggestive of either disorder. The exact relationship between HIV and lupus-like nephritis is unknown and the proper therapy for such patients is unclear. Our patient has maintained stable kidney function for more than 1 year with no specific therapy. The milder clinical phenotype and relatively benign course seen to date mirror the absence of proliferative features and chronicity on histology and may reflect the modulation of kidney pathology by posttransplantation immunosuppression.

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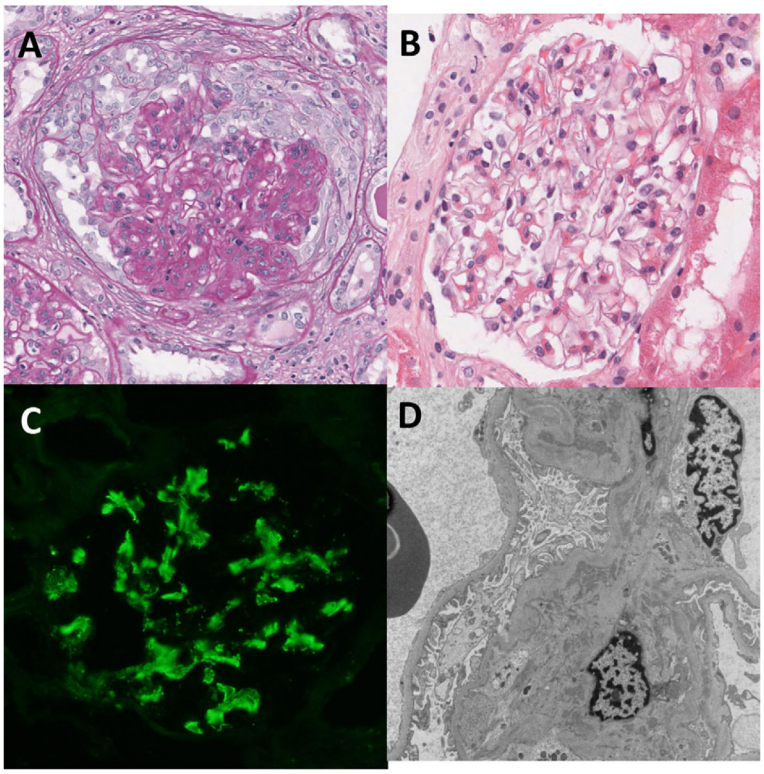

Figure 1.

Native and transplant kidney biopsy findings. (A) Light microscopy (native kidney) shows glomeruli with cellular crescents, mild to moderate mesangial widening, and mild to moderate mesangial and endocapillary hypercellularity. (Periodic acid–Schiff stain; original magnification, ×40.) (B) Light microscopy (transplant kidney) shows no significant glomerular pathologic abnormality. (Hematoxylin and eosin stain; original magnification, ×40.) (C) Immunofluorescence microscopy (transplant kidney) shows strong (3+) mesangial C1q positivity. (Original magnification, ×40.) (D) Electron microscopy (transplant kidney) shows mesangial electron-dense immune-type deposits.