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CASE REPORT

Diffuse infiltrative lymphocytosis syndrome presenting as renal failure in South African HIV-positive individuals: a single-centre case series

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ABSTRACT

Diffuse infiltrative lymphocytosis syndrome (DILS) in human immunodeficiency virus (HIV) infection presented most commonly with parotidomegaly and sicca symptoms in the pre-antiretroviral era. However, numerous clinical manifestations are possible due to the multi-organ nature of the CD8+ lymphocytic infiltration. Renal involvement is infrequently described, but common characteristics of a renal syndrome associated with DILS have been identified. This case series describes four South African HIV-positive patients with DILS, in whom renal failure was the sole clinical manifestation. As DILS responds well to antiretroviral and corticosteroid therapy, this series highlights the importance of considering this syndrome as a cause of renal failure in an HIV-positive patient.

Keywords: HIV, renal failure, diffuse infiltrative lymphocytosis syndrome.

INTRODUCTION

In 1987, the first case of extensive multi-system CD8+ infiltration was described in an HIV-positive male [1]. This Sjögren-like syndrome, subsequently termed diffuse infiltrative lymphocytosis syndrome (DILS), manifests as a CD8+ lymphocytic infiltration in multiple organs [2]. It commonly involves the salivary glands and lungs but has protean clinical manifestations including myositis, peripheral neuropathy, hepatitis, and pan-uveitis. There are also limited case reports of interstitial renal involvement [3,4]. The prevalence of DILS has declined with the widespread availability of antiretroviral therapy (ART) [5–9]. The proportion of patients with sicca symptoms has also declined, possibly contributing to under-diagnosis [7].

We describe four South African patients with clinical and histopathological features of a DILS-related nephropathy. None of these patients presented with the classical features of parotidomegaly or sicca symptoms but rather were found to have a CD8+ lymphocytic interstitial infiltrate on renal biopsy.

Case 1

A 36-year-old HIV-positive, ART-naïve male with a CD4 count of 912 cells/mm^3 presented with clinical features of pulmonary tuberculosis (TB), subsequently confirmed on sputum GeneXpert. His serum creatinine concentration on commencing treatment was 213 µmol/L. Shortly thereafter, he was admitted with malaise and oliguria. Clinically and radiologically his chest was clear, there was no hepatomegaly, lymphadenopathy or peripheral neuropathy. His creatinine had increased to 1419 µmol/L with severe metabolic acidosis requiring haemodialysis. Urine

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dipstick revealed 3+ blood, 2+ protein and a urine protein/creatinine ratio (UPCR) of 0.281 g/mmol. Urinary lipoarabinomannan (LAM) was negative. Ultrasonography showed enlarged (14.7 and 15.8 cm), echogenic kidneys with poor cortico-medullary differentiation. A renal biopsy demonstrated dense interstitial infiltration with T-lymphocytes, and CD8+ to CD4+ ratio >2:1, with markedly reduced serum CD4+ to CD8+ ratio of 0.18. There was no evidence of eosinophilia, acute tubular necrosis or granulomatous interstitial nephritis (GIN) on the renal biopsy. Tuberculous immune reconstitution inflammatory syndrome (IRIS) of the kidney was less likely as the patient had not yet been started on ART. A diagnosis of interstitial nephritis associated with DILS was made. The patient was started on dose-adjusted ART, TB treatment including rifampicin was continued and 1 mg/kg prednisone was initiated. There was a rapid decline in serum creatinine, and dialysis was discontinued within a week. On follow-up, his creatinine had decreased to 124 µmol/L.

Case 2

A 58-year-old HIV-positive male, with a CD4+ count of 204 cells/mm^3, was started on ART a month prior to presentation. He was known to be hypertensive, with clinical evidence of hypertensive heart disease, and had defaulted anti-hypertensive treatment when he presented with a serum creatinine concentration of 290 µmol/L. Urine dipstick revealed microscopic haematuria with trace proteinuria, and his UPCR was 0.05 g/mmol. Ultrasound revealed echogenic kidneys of 9.6 cm and 9.9 cm. The renal biopsy demonstrated a heavy interstitial infiltrate consisting of 80% CD8+ T-lymphocytes. Blood vessels showed advanced benign arterio-nephrosclerosis. No treatment with corticosteroids was initiated and ART was continued. His blood pressure was controlled and serum creatinine settled at 223 µmol/L.

Case 3

A 28-year-old HIV-positive, ART-naïve female with CD4+ count of 811 cells/mm^3 had recently started empiric TB treatment based upon constitutional symptoms and a chest radiograph suggestive of miliary TB. Her baseline creatinine was 67 µmol/L when tested at her local clinic. She was referred with pyelonephritis and sepsis and was treated appropriately with ceftriaxone. Splenic micro-abscesses and intra-abdominal lymphadenopathy on ultrasonography supported the suspicion of disseminated TB. A creatinine concentration of 156 µmol/L as well as bilaterally enlarged kidneys on ultrasound prompted a renal biopsy to investigate for HIV-associated nephropathy. Renal biopsy demonstrated collapsing focal segmental glomerulosclerosis as well as a heavy interstitial infiltrate of predominantly CD8+ T-lymphocytes. There were no granulomas or eosinophils seen. There was no eosinophilia on the differential white cell count. Lymphoma was excluded on subsequent bone marrow biopsy. The histology and low serum CD4+% of 18.7 (CD8+% not quantified) favoured the diagnosis of a DILS-related nephropathy. She was not treated with steroids but was started on ART. Her creatinine normalised to 92 µmol/L.

Case 4

A 29-year-old newly diagnosed HIV-positive male, with CD4+ count of 216 cells/mm^3, was admitted to the intensive care unit with severe, community-acquired pneumonia and acute kidney injury requiring dialysis. Tracheal aspirate culture was negative for TB. He was not on any medication prior to admission. Ultrasound demonstrated large, echogenic kidneys (13.1 and 12.5 cm) as well as hepatosplenomegaly. His serum creatinine peaked at 412 µmol/L. On urinalysis he had 3+ leucocytes and 3+ erythrocytes, with granular and waxy casts. UPCR was 1.30 g/mmol. Renal biopsy showed features consistent with HIVAN, severe tubular atrophy and fibrosis, and heavy CD8+-predominant interstitial lymphocytic infiltration. Once stabilised on ART, his creatinine settled at 115 µmol/L.

DISCUSSION

DILS is part of the spectrum of HIV-associated tubulointerstitial diseases [10,11]. Most cases of biopsy-proven interstitial nephritis in HIV are due to drugs [12] or TB, which produces a granulomatous interstitial nephritis [13]. HIV-associated nephropathy produces a diffuse plasmacytic interstitial infiltrate [14,15], which differentiates it from DILS in which the infiltration is T-lymphocyte predominant.

DILS-related nephropathy has few case descriptions in the literature. In a review of three case series, renal involvement was present in only 7% of patients [3]. Zafrani et al. described clinical and histopathological features characteristic of the renal syndrome associated with DILS [16]. Typical findings include enlarged kidneys and mild proteinuria. Renal biopsy features include acute tubulointerstitial nephritis with infiltration by a majority of CD8+ lymphocytes, without granulomas or glomerular involvement. Extensive damage may lead to interstitial fibrosis, tubular destruction and chronic kidney disease (CKD) [16].

Three of our patients had enlarged kidneys, while the fourth's kidney sizes were likely affected by concomitant

Table 1. Common characteristics of the DILS-renal syndrome documented in our patients.

	Case 1	Case 2	Case 3	Case 4
Biological findings				
CD4 count (cells/mm³)	912	204	811	216
High HIV viral load (VL)	All ART naïve or recently started on ART, so presumed high VL			
Serum CD8+ hyperlymphocytosis	Absolute CD8+ 2346 cells/mm³	ND	ND	ND
Polyclonal hypergammaglobulinaemia (Total protein)	>120 g/L	87 g/L	105 g/L	76 g/L (Albumin 14 g/L)
Acute renal failure (organic renal failure with acute flares)	✓ (possible background CKD)	✓ (background CKD)	✓	✓ (possible background CKD)
Functional tubular disorders (salt wasting, distal acidosis, mild grade proteinuria)	UPCR 0.281 (g/mmol)	UPCR 0.05 (g/mmol)	UCPR 0.26 (g/mmol)	UPCR 1.30 (g/mmol)
Leucocyturia, haematuria	✓	✓	✓	✓
Ultrasonography findings				
Kidney size (cm)	14.7; 15.8	9.6 ; 9.9	14.1; 13.0	13.1; 12.5
Kidney echogenicity	Echogenic	Echogenic	Echogenic	Echogenic
Renal biopsy findings				
CD8+ predominant T- lymphocyte interstitial infiltrates	✓	✓	✓	✓
Tubulitis	✓	✓	Not reported	✓
Tubular atrophy	Severe	Severe	Not reported	Moderate
Interstitial fibrosis	Moderate	Severe	Not reported	Moderate
Negative findings: absence of granuloma	✓	✓	✓	✓
Treatment				
Steroid-sensitive flares	✓	Not treated	Not treated	Not treated
Antiviral therapy	✓	✓	✓	✓

ND, not done; UPCR, urine protein/creatinine ratio; CKD, chronic kidney disease.

hypertensive nephrosclerosis. They all presented with leucocyturia, haematuria and varying degrees of proteinuria. Biopsy findings for all patients showed a dense mononuclear interstitial inflammatory infiltrate with moderate to severe interstitial fibrosis. There were focal areas of tubulitis and tubular atrophy. Immunostaining highlighted a CD8+-predominant T-cell infiltrate with a minor CD4+ component (<20%). The biopsy of two patients showed concurrent HIV-associated nephropathy, evidenced by collapsing focal segmental glomerulosclerosis. Interstitial granulomas were not identified in any of the biopsies, and other common causes of interstitial nephritis were excluded.

Extra-glandular manifestations, such as renal infiltration, may be more common in ART-naïve patients [17]. Given the varied and changing manifestations of the syndrome, some authors recommend moving to histological rather than clinical diagnosis [18]. Currently, no specific guidelines exist for the management of DILS-related nephropathy, but the first-line treatment for DILS is ART. This can improve circulating CD8+ lymphocytosis and tissue infiltration [19]. Patients established on effective ART may benefit from supplementary corticosteroids, which could produce partial or complete resolution of symptoms associated with organ infiltration [6,20]. However, there remains a high risk of relapse on corticosteroid withdrawal [16,21,22].

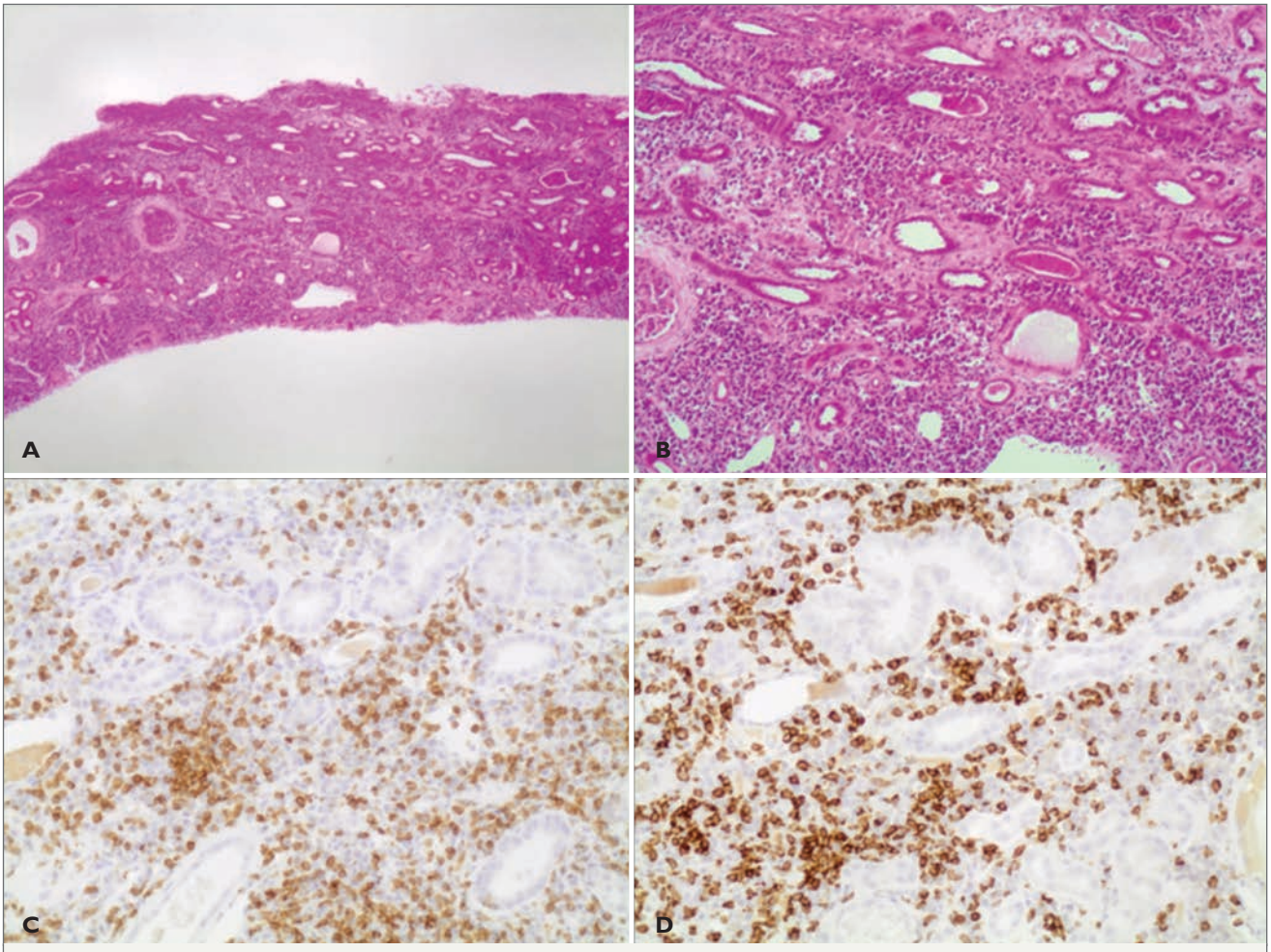

Figure 1. Renal biopsy findings for Case 1. The renal interstitium shows diffuse expansion by sheets of inflammatory cells with background interstitial fibrosis and tubular atrophy (panel A, H&E x40). The inflammatory infiltrate is composed predominantly of lymphocytes and plasma cells (B, H&E x100). Immunohistochemical staining of the inflammatory infiltrate highlights mostly (C) CD3+ cells (polyclonal rabbit antibody, diluted 1:300, Dako, Denmark) and (D) CD8+ (clone 4B11, diluted 1:20, Novocastra, UK) T-lymphocytes with only sparse CD20+ B-lymphocytes (not shown).

The patient in Case 1 exhibited a remarkable response to a combination of corticosteroids and ART. When Cases 2, 3 and 4 presented, case descriptions of renally-isolated DILS were relatively rare, and optimal management was not yet clearly defined in the literature. These three patients were therefore managed with ART alone as first-line treatment. Their outcomes were varied. Two patients returned to normal renal function, and the individual described in Case 2, who had significant hypertensive nephrosclerosis, had a stable creatinine of 223 µmol/L on follow-up. All four patients are currently well and following up at their primary care facilities from 2 to 9 years after their initial diagnosis.

CONCLUSIONS

This case series describes four patients with renal biopsy findings highly suggestive of DILS, yet without the classic parotidomegaly and sicca symptoms. In the ART era, the typical presentation of DILS may have changed, and the lack of salivary gland symptoms and signs should not deter the clinician from including DILS in the differential diagnosis of renal impairment in an HIV-positive patient. DILS should be suspected when diffuse T-cell lymphocytic infiltration is seen on renal biopsy, with immunostaining confirming CD8+ predominance. This case series, and existing evidence, have demonstrated that timely diagnosis and the addition of prompt corticosteroid treatment to ART may result in rapid improvement in renal function and could prevent progression to chronic kidney disease. This is important in a resource-scarce African setting where access to dialysis is limited.

Ethics approval was obtained from the University of Cape Town's Human Research Ethics Committee (HREC reference no. 491/2008).

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