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## A case of nephrotic syndrome secondary to HIV immune complex kidney disease

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### ABSTRACT

HIV immune complex disease of the kidney (HIVICK) is a rare but increasingly well-recognised cause of renal dysfunction and proteinuria in HIV-positive patients. A 56-year-old man with known HIV, diabetes mellitus type 2, liver cirrhosis and previous Hepatitis C virus (HCV) presented with a labile estimated glomerular filtration rate and significant proteinuria. Electron microscopy from a renal biopsy identified capillary wall deposition for IgG, IgM, Kappa, Lambda and focal C1q consistent with membranoproliferative glomerulonephritis (MPGN) and associated immune complex disease. A second opinion of the images confirmed the diagnosis of HIVICK. The increased recognition of HIVICK in HIV patients should prompt further research into the causes and treatment options available.

### *Implication for health policy/practice/research/medical education:*

Nephrotic syndrome and chronic kidney disease in patients with HIV can be due to a number of causes - both HIV-independent and HIV-associated. Complete suppression of HIV viral load does not eradicate the risk of an HIV-related nephropathy. The increased recognition of HIV immune complex disease of the kidney in HIV patients should prompt further research into the causes and treatment options available.

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### Introduction

The prevalence of renal impairment in HIV-positive patients ranges from 2.4% to 12% with proteinuria evident in 10% to 30% (1-3). Renal pathology may be the direct result of HIV infection as is the case in HIV-associated nephropathy (HIVAN) or due to HIV-independent causes such as diabetes mellitus, hypertension, intravenous drug use and adverse drug reaction (4). HIV immune complex disease of the kidney (HIVICK) contains several separate pathologies, including post-infectious glomerulonephritis (GN) and 'lupus-like' GN (5). HIVICK can present with proteinuria and kidney dysfunction (6). HIVICK was previously believed to preferentially afflict Caucasians, however more recent research has shown that it is also prevalent in the black African population, with a higher

incidence of HIVICK in black Africans than HIVAN (5,7). HIVICK is less likely than HIVAN to progress to end-stage renal failure (ESRF), but data on its response to antiretroviral therapy is lacking in terms of renal outcomes (8).

### Case Presentation

A 56-year-old Caucasian male was referred to nephrology in February 2018 with a history of fluctuating estimated glomerular filtration rate (eGFR) associated with significant proteinuria. He had a significant past-medical history of HIV (diagnosed in 1993, managed with darunavir/cobicistat, maraviroc and dolutegravir). Viral load had been consistently undetectable since July 2017. There was no history of any acquired immune deficiency syndrome

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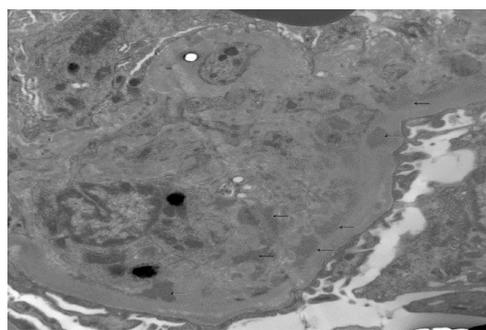
(AIDS)-defining illnesses. Additional past-medical history included type 2 diabetes mellitus (diet-controlled, with known peripheral neuropathy), hepatitis C (diagnosed in 2011, successfully treated with ledipasvir/sofosbuvir and ribavirin – viral load undetectable) and liver cirrhosis with portal hypertension. There was no recent history of herbal or recreational drug use. There was no history to suggest an in situ splenorenal shunt or chronic bacterial infection. He was otherwise asymptomatic without features of an autoimmune disorder or vasculitis. Blood pressure was 142/88 mmHg. Aside from splenomegaly and peripheral neuropathy, there were no clinical features of any significance on clinical examination.

### Investigations

Investigations showed a serum creatinine of 97  $\mu\text{mol/L}$  (eGFR 73.8 mL/min/1.73 m<sup>2</sup>) with a raised urine protein:creatinine ratio (PCR) of 301 g/mol (Table 1). Over the previous year, urine PCR results had ranged between 102-126 g/mol and serum albumin between 27-32 g/L. HbA1c had been elevated at 87 mmol/mol, however it improved to 38 mmol/mol through dietary intervention. There was no reduction in proteinuria despite the improved glycaemic control. He had thrombocytopenia with platelet count ranging from 92-104  $\times 10^9/\text{L}$  attributable to portal hypertension.

A renal autoantibody screen (including anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, anti-double stranded DNA and anti-glomerular basement membrane) was negative. Complement levels were normal and C3 nephritic factor was not detected. Alpha-fetoprotein level was not elevated. CD4 count was 216 cells/mm<sup>3</sup> in June 2018 with a viral load of <30 c/mL. Hepatitis C viral PCR was negative. An oesophago-gastroduodenoscopy was unremarkable.

A computerised tomography (CT) scan of thorax/abdomen/pelvis identified slightly atrophic kidneys with bilateral simple cysts, chronic liver cirrhosis and compensated portal hypertension with severe splenic varices. A whole-body positron emission tomography scan was performed to exclude chronic infection and malignancy, which identified increased uptake in the left maxillary sinus but no other significant abnormalities.



**Figure 1.** Renal biopsy highlighting capillary wall deposition for IgG, IgM, Kappa, Lambda and focal C1q under electron microscopy.

Neither scan identified any evidence of malignancy (HIV in particular is associated with various forms of lymphoma) (9).

The urine PCR peaked at 1051 g/mol however serum creatinine remained stable at 89  $\mu\text{mol/L}$ . A renal biopsy was performed in May 2018 which identified capillary wall deposition for IgG, IgM, Kappa, Lambda and focal C1q (Figure 1). The pattern was consistent with membranoproliferative glomerulonephritis (MPGN) with associated immune complex disease. A second opinion on the renal biopsy confirmed that the histological appearances were in keeping with HIVICK.

The patient's HIV team were consulted as to whether this could be a side effect of his HIV medications, with their opinion being that it was unlikely.

### Outcome and follow-up

In the weeks following the diagnosis of HIVICK, the patient became acutely unwell with an unrelated illness, which necessitated a period of time on intensive care. He has now been discharged from hospital to recover fully prior to consideration of any treatment regimens for HIVICK.

### Discussion

Causes of the nephrotic syndrome in a patient with HIV, HCV and diabetes mellitus can be multiple. Serological investigations excluded autoimmune disease (such as

**Table 1.** Timeline of basic investigations

| Date      | eGFR (ml/min/1.73 m <sup>2</sup> ) | Urea (mmol/L) | Creatinine ( $\mu\text{mol/L}$ ) | Urine PCR (g/mol) | Albumin (g/L) | HbA1c (mmol/mol) | Platelets ( $\times 10^9/\text{L}$ ) |
|-----------|------------------------------------|---------------|----------------------------------|-------------------|---------------|------------------|--------------------------------------|
| Feb. 2018 | 73.8                               | 4.2           | 97                               | 301               | 30            | 87               | 92                                   |
| Apr. 2018 | 65.9                               | 7.3           | 107                              | 467               | 32            | -                | 104                                  |
| Aug. 2018 | 81.5                               | 5.3           | 89                               | 1051              | 30            | 38               | 98                                   |
| Oct. 2018 | -                                  | -             | -                                | 611               | -             | -                | -                                    |
| Nov. 2018 | 72.1                               | 7.9           | 99                               | -                 | 23            | -                | 95                                   |

systemic lupus erythematosus; SLE) and imaging excluded paraneoplastic proteinuria (9). Diabetic nephropathy was excluded on renal biopsy as were medication-associated causes. Tenofovir has been linked with tubulopathy however the patient's current medications are not commonly known to cause tubulointerstitial nephritis (10).

HIVAN presents with significant proteinuria and progressive renal impairment with histological features of focal segmental glomerulosclerosis or interstitial nephritis (11). It is unlikely in those with normal CD4 counts and undetectable viral load.

Our patient had HIVICK which presents with a similar clinical picture of proteinuria and chronic kidney disease. HIV antigens and altered immune regulation contribute to circulating immune complexes in HIVICK (12). Histological examination demonstrates a basement membrane with a 'ball in cup' appearance, which has also been noted in lupus nephritis (12). A 'lupus-like' nephritis in the presence of HIV, without any clinical or serological evidence of SLE is in keeping with a diagnosis of HIVICK (13). HIVICK and HIVAN are not mutually exclusive diagnoses however and there may be histological features of both conditions (12).

A number of other immune complex mediated diseases have been identified in HIV patients including HIV associated membranous GN, membranoproliferative GN, mesangial proliferative GN and IgA nephropathy (12,13).

Although our patient had previously been co-infected with HCV, his viral PCR was negative and there is no link between HCV and HIVICK in the literature (14). Foy et al compared patients with HIVICK and HIVAN and found that the HIVICK group were more likely to be on antiretroviral therapy, had higher CD4 counts and lower viral loads, as is the case with our patient (8). There were also higher rates of diabetes and hypertension in the HIVICK group similarly to our patient (8). African-American ethnicity, high HIV RNA levels (>400 copies/mL) and advanced HIV were also shown to be associated with HIVICK (unlike in this case) (8). HIVICK has been shown to be less likely than HIVAN to progress to ESRF (14).

Treatment options are limited in HIVICK. Antiretroviral therapy can slow progression to ESRF however our patient had already been established on appropriate therapy (14,15). Blood pressure control and renin-angiotensin inhibition can reduce proteinuria (14). Immunosuppression is not beneficial (16).

## Conclusion

The increased recognition of HIVICK in HIV patients should prompt further research into the causes and treatment options available.

## Authors' contribution

ME and PL drafted the initial manuscript which was modified by AB. Literature review performed by PL and AB. Electron microscopy findings provided by ME. Additional insight provided by AB. All authors have reviewed and agreed on the final version of this manuscript prior to submission.

## Conflicts of interest

The authors declare no conflict of interest.

## Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. The patient has provided informed consent to publish as a case report.

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