NELL1-Positive HIV-Associated Lupus-Like Membranous Nephropathy with Spontaneous Remission

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Abstract
Introduction: Kidney biopsy findings in patients with human immunodeficiency virus (HIV) are diverse, and optimal therapy for the various immune complex diseases in the setting of HIV is unknown. Case Presentation: A man with well-controlled HIV developed nephrotic range proteinuria, and kidney biopsy revealed lupus-like glomerulonephritis with a predominantly membranous pattern of injury. He opted for conservative therapy and experienced spontaneous and sustained remission. Subsequent testing revealed neural epidermal growth factor-like 1 (NELL1)-positive glomerular immune deposits. NELL1-positive glomerular immune deposits were identified in a total of 2 of 5 tested HIV-associated membranous nephropathy (MN), which were morphologically dissimilar and one of which weakly co-expressed phospholipase A2 receptor (PLA2R). Discussion: This case suggests potentially different outcomes in patients with immune complex diseases in the setting of HIV based on disease etiology and histopathology. HIV-associated MN is occasionally NELL1-positive.

Introduction
A broad spectrum of kidney biopsy findings can be seen in patients with human immunodeficiency virus (HIV), including immune complex disease and HIV-associated nephropathy, a rapidly progressive form of collapsing focal segmental glomerulosclerosis more commonly seen in the setting of acquired immunodeficiency syndrome in patients with APOL1 high-risk alleles [1, 2]. Tenofovir toxicity and kidney injury due to various underlying conditions such as diabetic nephropathy, focal segmental glomerulosclerosis, or other glomerular or tubulointerstitial diseases can also be seen [1]. Immune complex diseases in the setting of HIV encompass a vari-
ety of glomerulonephritis (GN) patterns and etiologies: infection-related or post-infectious GN, IgA nephropathy, lupus-like GN, membranous nephropathy (MN), membranoproliferative GN, and mesangial proliferative GN [1, 2]. Given this diversity, optimal treatment for HIV-associated immune complex disease is unknown and depends in part on the clinical scenario, pathology, and etiology. Herein, we describe a patient with well-controlled HIV who developed lupus-like GN with a membranous pattern of injury who declined immunosuppressive therapy and experienced a spontaneous remission which was sustained at 7 years.

**Case Report**

**Clinical Presentation**

A 65-year-old Caucasian gentleman presented with 9 g proteinuria, fatigue, loss of weight 20 pounds, joint aches, and distorted sense of taste. He had been diagnosed with HIV 34 years earlier and had taken part in a clinical study in which he was determined to be a chronic non-progressor of HIV and had not required any antiviral therapy until 2 years prior to presentation. At that time, he was initiated on antiretroviral therapy (ART) with elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate due to declining CD4 counts and rising viral load. His other medical history included hypothyroidism, but he had no hypertension or diabetes.

Examination revealed a well-appearing man without hypertension (blood pressure 120/64 mm Hg) or tachycardia (pulse 64/min), and no clinical features of nephrotic syndrome. Laboratory studies demonstrated hypoalbuminemia (2.8 gm/dL) and low white blood cell count (4,700/μL) with otherwise normal blood count and basic chemistry panel. HIV-1 RNA by PCR was <20/μL, and absolute CD4 count was 341 cells/μL. Serum creatinine was 1.0 mg/dL. Urine analysis showed 0–2 RBC/HPF and 0 white cells, and 24-h urine protein was quantified at 9,390 mg. Anti-nuclear antibody, antineutrophil cytoplasmic antibodies, complement 3, complement 4, Sjogren’s antibodies (SS-A, SS-B), rapid plasma reagin, hepatitis B surface antigen, hepatitis C antibody studies were negative/normal. The primary clinical concerns were for immune complex diseases in the setting of HIV and HIV-associated collapsing glomerulopathy, the latter of which was considered less likely in this patient with well-controlled HIV and Caucasian background. Kidney biopsy was performed to determine the cause of nephrotic range proteinuria.

**Kidney Biopsy**

Kidney biopsy (Fig. 1) demonstrated MN with segmental subepithelial eosinophilic immune deposits on the outer aspect of
the glomerular capillary loops. There was no mesangial or endo-
capillary hypercellularity, crescents, or segmental sclerosis, and
minimal chronic injury in the tubulointerstitium. Immunofluo-
rescence revealed a nearly “full house” pattern of glomerular cap-
illary wall immune complex deposition composed of IgG (3+),
IgM (1+), kappa and lambda light chains (both 3+), C3 (1–2+),
and C1q (2+). There was no significant staining for IgA and no
extraglomerular staining. Phospholipase A2 receptor (PLA2R)
was negative, and IgG subclass evaluation revealed 3+ staining
for each of IgG1, IgG2, IgG3, and IgG4. Electron microscopy re-
vealed irregularly distributed subepithelial immune deposits
with occasional subendothelial and mesangial immune deposits.
No deposit substructure nor definitive endothelial tubuloreticu-
lar inclusions were identified. Subsequent testing for other anti-
gens in MN revealed that the immune deposits stained for neural
epidermal growth factor-like 1 (NELL1) and were negative for
exostosin 1/2 and thrombospondin type 1 domain containing 7A
(THSD7A).

Follow-Up
The patient was started on losartan. Malignancy workup in-
cluding colonoscopy (prior to biopsy), prostate-specific antigen
testing, and subsequent fecal immunochromatic test was negative.
Mycophenolate mofetil was offered due to presence of lupus-like
MN, but after extensive discussions, he opted not to take this or
other immunosuppressive medications. He continued on losartan
and his herbal supplements, none of which contained steroids nor
lipoic acid (full list with ingredients available in online suppl. Ma-
terial; see www.karger.com/doi/10.1159/000525541 for all online
suppl. material). His proteinuria improved from 9 g to 6 g in 2
months’ time and to less than 1 g at 7 months (Fig. 2). His antiviral
therapy was switched to dolutegravir, abacavir, and lamivudine
subsequently. At 7 years since his initial presentation, he continues
to have normal renal function with no proteinuria.

Discussion
In this report, we describe a spontaneous and sus-
tained remission of HIV-associated lupus-like GN with
a predominantly membranous pattern of injury in a pa-
tient with well-controlled HIV. We also identify NELL1
as a glomerular antigen in a subset of HIV-associated
MN, which to our knowledge has not previously been
reported.

Given the finding of NELL1-positive glomerular im-
une deposits in this patient, an additional 4 cases of
HIV-associated MN (previously reported in reference
[3]) were stained for NELL1, one of which was positive,
yielding a total of 2 of 5 tested HIV-associated MN which
expressed NELL1. This additional NELL1-positive HIV-
associated MN occurred in a similar context of a patient
on ART with an undetectable HIV viral load but differed
from the reported patient in that it lacked any glomerular
staining for C1q, had IgG4 dominant immune deposits,
and the deposits were diffusely distributed along subepi-
thal aspects of glomerular basement membranes with-
out mesangial or subepithelial immune deposits. It also
demonstrated weak, finely granular but incomplete capil-
lar wall staining for PLA2R (Fig. 3; online suppl. Mate-
rial), although anti-PLA2R antibodies were not detect-
able in the patient’s serum [3].

Approximately 50% of HIV-associated MN cases have
tissue reactivity for PLA2R antigen [1, 3], which is not al-
ways accompanied by detectable serum anti-PLA2R anti-

Fig. 2. Spontaneous and sustained remis-
sion of proteinuria, with stable kidney
function.
bodies [3]. NELL1-positive MN has also been associated with malignancy [4], alpha-lipoic acid use [5–7], graft versus host disease after hematopoietic stem cell transplantation [8], and apparently primary MN [9, 10]. Dual PLA2R and NELL1+ MN have been identified in 1 patient with detectable serum anti-PLA2R but not anti-NELL1 antibodies [10], and in one case based on mass spectrometry [11] but is considered rare. Whether this apparent dual-positivity is due to a true biologic process or an artifact of technical or interpretive factors is unknown. Our dual-positive case had pathologic features which differed from the reported patient and were more similar to other cases of PLA2R-positive MN except for the presence of incomplete glomerular capillary wall staining for PLA2R. This highlights the importance of considering additional MN antigen testing in certain clinical scenarios, particularly in patients with underlying conditions or negative serum anti-PLA2R.

Although this biopsy had some “lupus-like” features [12], – nearly “full house” immune complex deposition and subepithelial, subendothelial, and mesangial deposits – it lacked glomerular proliferative or sclerosing features, and the patient was on ART with undetectable viral load at time of biopsy. Compared with other HIV-associated immune complex and nonimmune complex kidney diseases, HIV-associated MN more often occurs in patients on ART therapy or with low HIV or undetectable viral loads [1, 3, 13, 14], suggesting that immune system dysregulation rather than active HIV infection plays a role in the development of MN. Finally, from a therapeutic standpoint, this case highlights an example of an HIV-associated lupus-like MN without proliferative features treated conservatively with a sustained spontaneous remission. The patient’s disease course more closely matched the good prognosis of NELL1-MN, highlighting the importance of distinguishing the etiology, histopathology, and antigen, if possible, in the various immune complex diseases associated with HIV.

Fig. 3. Apparently dual PLA2R and NELL1 tissue-positive HIV-associated MN with MN (a) with subtle thickening of capillary loops and no proliferative features (PAS. ×200), granular peripheral capillary wall staining IgG, IgG4 dominant (b). Electron microscopy with diffuse subepithelial immune deposits (transmission electron microscopy, direct magnification, ×2,000, c). Glomerular immune deposits showed weak, incomplete reactivity for PLA2R by immunofluorescence (d) and immunohistochemistry (e), with strong immune complex staining for NELL1 (×200).
Statement of Ethics

The patient has given written informed consent to publish this case. Collection of this data is approved by the OHSU Institutional Review Board (IRB, Study 17467).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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