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APOL1 Variants may induce HIVAN during HIV Primary Infection

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Running head: Severe HIVAN during primary HIV infection

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Human Immunodeficiency Virus Associated Nephropathy (HIVAN) is still associated with high mortality, [1] and is usually a late complication of HIV chronic infection. [2] Since 2010, a link has been strongly established between APOL1 genetic variants and HIVAN, especially in the African population.[3]

A middle-aged man from Ivory Coast was admitted to hospital for a flu-like illness lasting for one month. He had already received several antibiotic regimens and previous malaria and HIV tests were negative. He had been on amlodipine/valsartan for many years for hypertension and his plasma creatinine level one month before was 1.25 mg/dL (110 µmol/L).

His weight had increased from 101 to 113 kg with pitting oedemas in the legs, and frothy urine for one month. Diffuse small peripheral lymphadenopathies were present. Clinical examination was otherwise normal.

Biological assessment showed an acute kidney injury with indication for dialysis: serum creatinine: 20.3 mg/dL (1781 µmol/L); blood urea nitrogen: 40.7 mmol/L; potassium, 5 mmol/L; carbon dioxide, 15 mmol/L, and a nephrotic syndrome with low serum albumin (1.3g/dL), high level proteinuria (7 g per day) and urinary protein/creatinine ratio: 1.72. Ultrasound found normal-sized hyperechogenic kidneys (12 cm each).

A renal biopsy showed typical HIVAN: one third of the glomeruli were sclerotic with all but one displaying a collapsing focal segmental glomerulosclerosis

(FSGS) with hypertrophic podocytes (figure 1A). The tubulointerstitial area revealed many cystic tubular lesions associated with a moderate inflammatory infiltrate (figure 1B). Acute tubular necrosis lesions and a discreet patchy fibrosis were also present. The immunofluorescence study was negative for IgA, IgG, IgM, C3, C1q, and albumin.

The HIV test (ELISA) confirmed with a Western blot (New Lav Blot / BioRad) returned positive. The p24 antigen was negative. The initial CD4 count was 594 cells/mm^3 (17%) and the plasma HIV-1 RNA was 1.2 million (6.04 log) copies/mL. The patient tested negative for syphilis, hepatitis B and C and opportunistic infections except for a cytomegalovirus (CMV) replication (3 log DNA copies/mL). The HIV-1 strain was a CRF02_AG subtype with a CCR5 tropism, and the genotyping assay displayed no resistance-associated mutation.

Antiretroviral therapy (ART) was quickly initiated with raltegravir and etravirine with addition of abacavir to the ART regimen when HLA B5701 returned negative. Dialysis was continued for 2 weeks. Considering the severity of renal failure and the nephrotic syndrome, the patient received both angiotensin-converting enzyme (ACE) inhibitors and corticosteroid therapy. Ten days after treatment introduction, plasma creatinine decreased and stabilized at about 2.3 mg/dL (200 μmol/L); protein/creatinine ratio also decreased to 0.46.

After six weeks of treatment, the HIV-1 load decreased to 449 copies/mL. The CD4 count increased to 1063 cells/mm^3 (45%) with a CD4/CD8 ratio of 1.18 and lymphadenopathy disappeared.

To confirm a recent HIV infection, we used both a supplemental Western blot (WB) assay (HIV Blot 2.2, MP Biomedicals, Singapore) and an enzyme immunoassay for recent infection (IDE-V3) .[4] The WB showed the presence of antibodies to GP160, GP120 and p24, weak reactivity towards the reverse transcriptase (P66/51) and GP41, and a lack of anti-integrase (p31) (figure 1C). This profile corresponds to Fiebig stage V.[5] The value of p (probability of being classified as a non-recent seroconverter) in the IDE-V3 assay was 0.016, a very low value consistent with a recent HIV infection.[4]

Analysis of the APOL1 gene showed that the patient was carrying two allelic variants called G1 and G2, already known to predispose to HIVAN and FSGS. The odds ratio to develop HIVAN when carrying two APOL1 variants (G1 and/or G2) is estimated to be 29.[3]

HIVAN is generally recognized as a complication of advanced HIV disease, with CD_4 count <200 cells/mm^3 characterized by rapidly progressive renal failure, proteinuria or nephrotic syndrome, urinary sediment, ultrasound finding enlarged, highly echogenic kidneys.[6] Nevertheless, the definitive diagnosis of HIVAN is based on histological criteria.

In our case, renal biopsy was consistent with typical HIVAN as well as the improvement of renal function with efficient ART, ACE inhibitors and corticosteroids.[7]

The unusual fact was the recent negative HIV test but the Fiebig stage V profile and the IDE-V3 assay confirmed the recent infection.

Another pre-existing cause of glomerulopathy, such as focal segmental glomerulosclerosis cannot be excluded here but is unlikely. CMV-induced FSGS has rarely been described, but the immunohistochemical study on the biopsy was negative for CMV and CMV viraemia remained stable during renal function improvement.

Rare cases of HIVAN during primary infection have been described. [8, 9, 10] Three cases were published in the early 2000s, when analysis of allelic variants of the APOL1 gene was not available. Therefore, to the best of our knowledge, this is the first report of a man carrying two APOL1 variants with HIVAN during a recent HIV infection.

This case illustrates that in patients with significant genetic risk, HIVAN may occur during primary HIV infection. Diagnosis should not be delayed to allow concomitant antiretroviral therapy and renal specific management.

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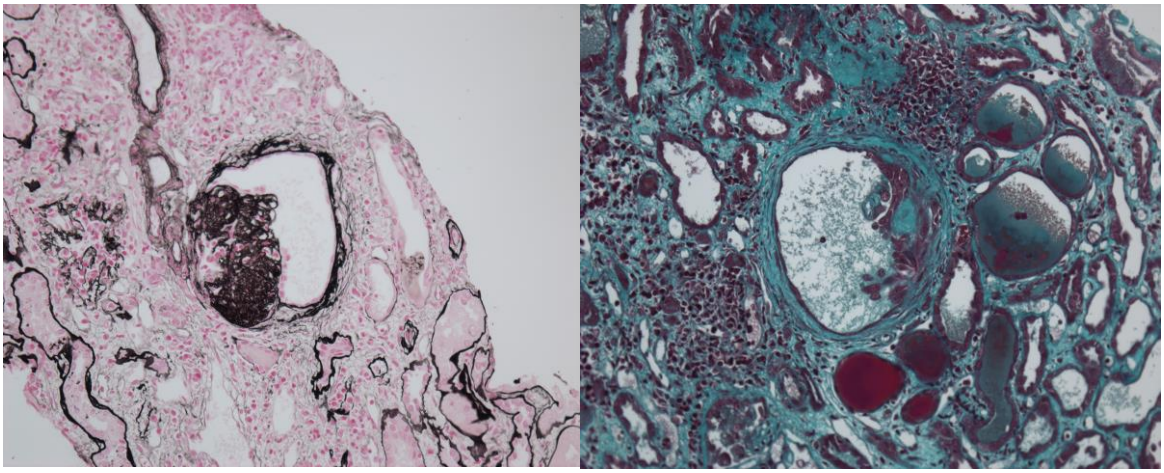
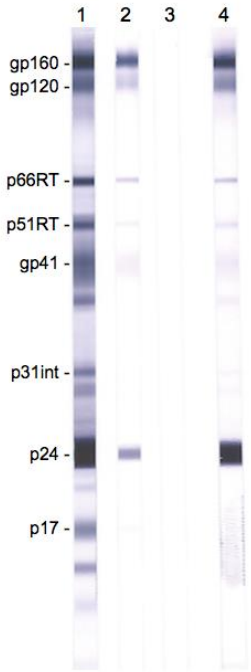
Figure 1.A **1.B**





1.C

Legends

Figure 1.A: Kidney biopsy: Focal segmental glomerulosclerosis with severe retraction of the flocculus, Periodic acid Schiff coloration. (magnification X100)

1.B: Kidney biopsy: Empty glomerulus, interstitial inflammation, cystic tubular dilatation. Masson trichrome. (magnification X100)

1.C: Western blot analysis of the serum sample collected at entry. Lane 1: HIV-1 positive control; lane 2: HIV-1 weak positive control; lane 3: negative control; lane 4: patient's serum.