Tuesday Conference
7/23/2013

Hasan Fattah
• 48 AA male, PMH: HTN, proteinuria since 2009, sent from primary clinic for high Cr evaluation (7.1), last known of 1.1 in 2010 associated with sub-nephrotic range proteinuria, and hematuria.

• No other PMH, allergies, meds, or new drugs

• ROS negative

• FH mother, and an uncle with kidney disease required RRT, no known etiology ? HTN
• Exam:
  Vitals: BP: 150/95  p: 60
  CV, and pulm grossly unremarkable. No edema, or skin rash.

• Labs:
  BMP upon referral from clinic:
  Na: 137  K: 5.1  CO2: 19  BUN: 51  Cr: 6.7  Ca: 8.6
  alb: 4.2  LDL: 134
  remained stable throughout hospital stay
• UA: moderate blood 2+, protein: 3+, no WBC
• U p/c: 2 g/g, U alb/Cr: 1340 mg/g
• Urine sed: few hyaline casts, no RBC’s.
• Hep B/C neg
• C3/C4: normal  ANA: neg, dsDNA: neg
• HIV: positive, confirmed
• Kappa: 650  lambda: 508  R: 1.2
• SPEP/UPEP: unrevealing
• SIF/UIF: no bands
• Renal US: normal size kidneys  9.5 x9.7 cm
• HIV-related renal diseases are the third leading cause of end-stage renal disease (ESRD) among African Americans aged 20 to 64 years

USRDS 1999 Annual Data Report

• The reported incidence of renal disease varies between 2% and 10%

Schoenfeld Am J Kidney Dis 1990

• spectrum of renal diseases that complicates HIV infection:
  – (HIVAN)
  – Non-HIVAN: includes amyloidosis, MCD, cryoglobulinemia, and various forms of IC GN, such as IgA nephropathy, membranous nephropathy, and MPGN
OBJECTIVES

• Epidemiology
• Renal disease spectrum and clinical course
• Pathogenesis
• Treatment
Epidemiology:

- a multicentric study of 60 patients from Paris hospitals: Patients were divided in two groups according to their ethnic origin (29 black patients and 31 white patients)
- The aim of this report is to describe the renal lesions encountered in HIV-infected patients in France and to compare them to the data originating from North America

Nochy et al NDT1993
FSGS was more frequent in black than in white patients (84% versus 11%, P *).

(ICGN) is a common finding in both series (45% and 20% in white and black patients respectively).

Ten patients (4 black and 6 white) had glomerular lesions similar to those seen in lupus nephritis.
A South African perspective

- retrospective cohort included all patients with documented HIV infection who underwent renal biopsy from 1st January 2003 to 31st December 2004, and compared to with an HIV-negative 'control' group biopsied during the same time

• Classic HIVAN: 27% pts,
  – pathology: FSGS with or without an associated collapsing component, Mesangial hyperplasia, overlying visceral epithelial cell prominence, interstitium with microcystic change of the PT, with varying degrees of IF/TA
  – Clinical: substantial proteinuria (11.8 g/day), advanced renal failure, and low CD4 counts
• HIVICK: 21%
  – Pathology: immune deposits within the mesangial and paramesangial regions, features between incompletely expressed PI and membranous, microcystic change of the tubular profiles.
  – IF: varying staining patterns, Several showed a ‘full-house’ ‘lupus-like’ pattern.
  – Clinical: similar to those with ‘classic HIVAN’, but less proteinuria (4.3 vs 11.8 g/day) with better creatinines on presentation.
• Membranous glomerulopathy: 13%
  – Pathology:
  – Clinically: heavy proteinuria with marked renal impairment, Two patients were Hepatitis B positive.

• Mesangial hyperplasia: 6%
  – low CD4 counts (average 157 cells/cm³)
  – high Cr, and heavy proteinuria (6.9 g/day)
  – ?evolving HIVAN

• Other glomerulonephritides.
Table 1 | Clinical characteristics of all HIV-positive patients who were biopsied

<table>
<thead>
<tr>
<th></th>
<th>HIVAN</th>
<th>ICD</th>
<th>Membranous</th>
<th>PIGN</th>
<th>Mes prolif</th>
<th>IgA</th>
<th>Other GN’s</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>27</td>
<td>21</td>
<td>13</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Sex (females)</td>
<td>13</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 (9)</td>
<td>35 (9)</td>
<td>34 (8)</td>
<td>36 (8)</td>
<td>34 (11)</td>
<td>32 (10)</td>
<td>27 (6)</td>
<td>37 (9)</td>
</tr>
<tr>
<td>Bpysys</td>
<td>131 (30)</td>
<td>132 (30)</td>
<td>143 (34)</td>
<td>136 (33)</td>
<td>113 (16)</td>
<td>121 (29)</td>
<td>133 (17)</td>
<td>152 (50)</td>
</tr>
<tr>
<td>Bpdiast</td>
<td>80 (17)</td>
<td>80 (19)</td>
<td>87 (23)</td>
<td>82 (27)</td>
<td>67 (7)</td>
<td>81 (17)</td>
<td>78 (8)</td>
<td>88 (44)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>770 (506)</td>
<td>493 (387)</td>
<td>713 (707)</td>
<td>319 (478)</td>
<td>273 (214)</td>
<td>507 (529)</td>
<td>343 (468)</td>
<td>1317 (87)</td>
</tr>
<tr>
<td>CD4 count</td>
<td>149 (182)</td>
<td>118 (85)</td>
<td>327 (269)</td>
<td>296 (117)</td>
<td>157 (156)</td>
<td>216 (192)</td>
<td>358 (193)</td>
<td>221 (132)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>11.8 (10.3)</td>
<td>4.3 (5.4)</td>
<td>6.8 (5)</td>
<td>3.5 (1.7)</td>
<td>6.9 (6.6)</td>
<td>6 (6)</td>
<td>6.4 (5.5)</td>
<td>3.0 (1.0)</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>21 (9)</td>
<td>29 (8)</td>
<td>27 (9)</td>
<td>23 (6)</td>
<td>19 (9)</td>
<td>27 (8)</td>
<td>24 (9)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.7 (2.8)</td>
<td>4.9 (2)</td>
<td>6.0 (2.4)</td>
<td>3.8 (0.8)</td>
<td>5.9 (2.4)</td>
<td>3.2</td>
<td>7.1 (3)</td>
<td>4.7 (1.9)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>4 out of 23</td>
<td>1 out of 18</td>
<td>2 out of 12</td>
<td>1 out of 7</td>
<td>1 out of 4</td>
<td>0 out of 5</td>
<td>2 out of 7</td>
<td>0 out of 8</td>
</tr>
<tr>
<td>Hepatitis C antibodies</td>
<td>0 out of 23</td>
<td>0 out of 18</td>
<td>1 out of 12</td>
<td>0 out of 7</td>
<td>0 out of 4</td>
<td>0 out of 5</td>
<td>0 out of 7</td>
<td>0 out of 8</td>
</tr>
<tr>
<td>Anti nuclear factor</td>
<td>0 out of 17</td>
<td>0 out of 13</td>
<td>1 out of 10</td>
<td>0 out of 4</td>
<td>1 out of 3</td>
<td>0 out of 3</td>
<td>2 out of 7</td>
<td>0 out of 4</td>
</tr>
</tbody>
</table>

Treatment: ACE inhibitors
- ACE inhibitors | 16 | 17 | 12 | 4 | 4 | 2 | 7 | 6 |
- Prednisone      | 4 | 2 | 4 | 0 | 2 | 0 | 3 | 0 |
- Simvastatin     | 9 | 5 | 6 | 1 | 2 | 0 | 4 | 3 |
- HAART            | 3 | 4 | 0 | 0 | 0 | 0 | 0 | 1 |

Follow-up (weeks) | 17 (23) | 14 (16) | 24 (29) | 28 (29) | 22 (30) | 17 (16.8) | 24 (16) | 23 (30) |
Lost to follow-up | 9 | 3 | 2 | 2 | 3 | 0 | 1 | 3 |
Alive             | 5 out of 18 | 9 out of 18 | 4 out of 11 | 3 out of 6 | 1 out of 3 | 1 out of 5 | 6 out of 8 | 3 out of 7 |

ACE, angiotensin-converting enzyme inhibitor; HAART, highly active antiretroviral therapy; HIVAN, HIV-associated nephropathy; ICD, immune complex disease; PIGN, post-infectious glomerulonephritis; Mes prolif, immune complex-negative mesangial proliferation; IgA, IgA nephropathy; other GN’s, other glomerulonephritides; other, other renal diseases.
P=0.006; P=0.003; P-values only shown where < 0.05.

*Positive results out of those whose relevant information was available (i.e. some data missing in records).
clinical epidemiology and course

- retrospective cohort study included HIV patients underwent renal biopsy at six major medical centers in US.

- The risk factors, clinical course, and potential modifying factors, including CD4+ count, HIV-1 RNA level, and the use of antiretroviral medications examined among the spectrum of renal diseases that complicates HIV infection.

## Epidimilogy and clinical course

Patient characteristics at time of kidney biopsy

<table>
<thead>
<tr>
<th></th>
<th>HIVAN</th>
<th>Non-HIVAN lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>42</td>
<td>13 ICGN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 Membranous N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 Diabetic N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 MPGN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 TIN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Amyloid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 FSGS without HIVAN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 MCD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Acute renal failure related to indinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 IgA nephropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Chronic pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>HIVAN</td>
<td>Non-HIVAN lesions</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>7/35</td>
<td>9/38</td>
</tr>
<tr>
<td>RACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>IVDU</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Hepatitis C status</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Hepatitis B status</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Cr CL mL/mina</td>
<td>39.0 (5.3)</td>
<td>60.6 (5.8)</td>
</tr>
<tr>
<td>Use of ART</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>HIV-1 RNA detectable</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>CD4+ count</td>
<td>187 (29)</td>
<td>287 (38)</td>
</tr>
<tr>
<td>Use of ACEI/ARB</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>
Time to initiation of renal replacement therapy from time of renal biopsy among patients with HIV-associated nephropathy (HIVAN) and with lesions other than HIVAN.

![Graph showing time to initiation of renal replacement therapy](image)

$P = 0.002$
Multivariable model of associations between clinical and demographic variables and time to initiation of renal replacement therapy among the entire cohort

<table>
<thead>
<tr>
<th>Lesions other than HIVAN vs. HIVAN</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.33</td>
<td>(0.15–0.71)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The type of renal disease (HIVAN vs. other) interacted significantly with HIV-1 RNA level and the use of antiretroviral therapy EVEN with sensitivity analysis (P = 0.0001 and 0.006, respectively)

<table>
<thead>
<tr>
<th>HIV-1 RNA (nondetectable vs. detectable)</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.16</td>
<td>(0.02–1.18)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Kidney bx:

• Light: BM appears prominent, numerous holes, spikes, moderate mesangial proliferation, IF 40%, severe interstitial lymphoplasmacytic infiltrate.

• IF: granular capillary and mesangial staining for IgG 3+, C3 2+, C1q 2+, kappa, and lambda 2+

• EM: frequent sub-epithelial/intra-membranous and mesangial IC deposits, rare TRI
HIVAN

- Rapid progression to ESRD
- Large, echogenic kidneys
- Advanced HIV
- Almost exclusively in blacks
- Positive impact of ART.
HIV and IC renal disease’’HIVICK’’

• HIV-associated immune complex renal Disease
• HIV-associated IgA Nephropathy
• Membranoproliferative Glomerulonephritis
• Postinfectious glomerulonephritis
• Membranous nephropathy
• Lupus-like glomerulonephritis
• Cryoglobulinemic Glomerulonephritis
• Immunotactoid glomerulopathy
• Fibrillary glomerulonephritis
• Nochy et al found 10 cases of lupus-like GN in their series of 60 HIV-infected patients from Paris.
• Haas et al identified 14 cases of lupus-like glomerulonephritis out of 77 renal biopsies performed in HIV-infected patients over a 5-year period in Baltimore.
• The histopathology is characterized by focal and diffuse proliferative glomerulonephritis on light microscopy.
• Immunofluorescence is unique with a “full house pattern” of C1q, IgG, IgM, IgA, C3, lambda, and kappa deposits.
• The clinical signs usually include nephrotic range proteinuria and severe renal failure.
• Patients typically are resistant to therapy, test negative for ANA, and anti-DNA antibodies, and have a poor 1-year renal survival.
• Thirteen of 14 cases of lupus-like glomerulonephritis in the Baltimore cohort were African American, which runs counter to the notion that Caucasians are more likely to develop immune complex glomerulonephritis.
• The relationship of this disorder to HIV infection remains unknown, and the proper therapy for such patients remains unclear and largely unevaluated.
HIVAN pathogenesis: HIV genetics

• In HIVAN patients and the murine model, HIV-1 mRNA is expressed in both renal glomerular and tubular epithelial cells.
• replicates in the renal epithelial compartment and the kidney serves as a reservoir for HIV even when undetectable in plasma

Nat Med 2002

• Nef→ in vivo podocyte proliferation

HIVAN pathogenesis: host genetics

• GWAS implicates a locus on chromosome 22
  – MYH9
  – APOL1

Kopp et al. nature Gen 2008
HIVICK pathogenesis

- Not well understood
- The frequent occurrence of hypergammaglobulinaemia in HIV patients suggest a pathogenic role of polyclonal B cell activation.
- Thus the occurrence of renal disease in HIV-infected patients is independent of the degree of immunosuppression and is related to a number of factors, including ethnic background, intensity of B cell activation, and concurrent viral or bacterial disease.
Figure 4. In situ hybridization for HIV-1 mRNA in HIVAN. Adapted from Bruggeman et al.
• large body of evidence from experimental models suggests loss of podocytes over a certain threshold induces glomerulosclerosis.

• Podocyte number is also reduced in proportion to the severity of injury and degree of proteinuria, and predicts progression in patients with diabetic nephropathy, IgA nephropathy, and FSGS.

• Finally, mutations that produce a glomerulosclerosis occur exclusively among genes expressed by the podocyte

• Regression of renal disease with remodeling of glomerular architecture is observed in pancreatic transplant patients with type 1 diabetes after 10 years of normoglycemia and in patients treated chronically with ACE inhibitors.

• Taken together, these results imply there are stem cells in adult glomeruli with the potential to regenerate podocytes
Glomerular epithelial stem cells regenerate podocytes.

Podocyte loss is a central determinant of progression to glomerulosclerosis.

Lasagni L, and Romagnani P JASN 2010;21:1612-1619
Factors influencing the outcome of the regenerative process may be the type, extension, or localization of podocyte injury, the age of patients, or patients' genetic background.

null alleles for the cell cycle inhibitor, p21
Dysregulated glomerular epithelial stem cells create their own lesions.

Lasagni L, and Romagnani P JASN 2010;21:1612-1619
hyperplastic intraglomerular lesions consisted of high numbers of cells (range 12 to 59). Triple-label IF demonstrated:

1- 50 to 75% of total cells represented immature progenitors, expressed CD133 and CD24 but not nestin or PDX.

2- In addition, tuft podocytes, expressing nestin or PDX in the absence of CD24 and CD133, represented 10 to 40% of total cells.

3- Finally, a population representing 2 to 15% of the cells were CD133+CD24+nestin +
• Recently, biopsies from individuals with HIV-associated and idiopathic collapsing glomerulopathy showed elevated TERT expression in podocytes

• Shkreli et al found that TERT overexpression led to activation of Wnt signaling

• inhibition of the Wnt pathway in the inducible TERT-transgenic model and in HIV-transgenic mice significantly improved the glomerular phenotype and reduced proteinuria

Treatment:

• Contribution of the virus?
• Contribution of the host immune responses?
• clear role of HIV in pathogenesis
• May regress with ART
• Is an indication for ART.
Figure 2. End-stage renal disease (ESRD) due to AIDS nephropathy and deaths in African Americans with AIDS. Data adapted from 2001 USRDS annual report (21) and the 2001 CDC HIV/AIDS Surveillance Report (23).


©2002 by American Society of Nephrology
• Role of adjunctive therapy
  – Uncontrolled studies support use of ACE
  – Anecdotal use of steroids: AE were common