Liver disease in the HIV infected patient – not always what it seems

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Causes of liver disease in patients with HIV infection:

- HDV
- HBV
- HAV
- HCV
- Opportunistic infections
- Alcohol
- NAFLD
- Insulin resistance and dyslipidaemia
- cART (NNRTIs, NRTIs, or protease inhibitors)
- Immune reconstitution

Hepatocellular carcinoma
Case 1

A 26 yr old female presenting with jaundice. Fatigue, abdominal pain, dark urine and pruritus.

PMH: HIV infected diagnosed in Feb 2011.
Current: CD4 420   Nadir: CD4 274
TDF/3TC/EFV May 2013 uneventful course until August 2013.
SH: No current ETOH or use of traditional meds
Past ETOH misuse.
Case 1

OE: Deep jaundice. No ascites, tender along the liver edge.
No palpable spleen.
No liver flap, no evidence of encephalopathy
Laboratory Results:
T Bili 72, C Bili 66, ALP 1198, GGT 3369, ALT 249, INR 1.2., platelets 240
Hepatitis C antibody negative, HEV PCR and antibody negative, HBsAg positive, antiHBe positive, HBV VL ND
ASMA neg, ANA Pos 1:160, IgG 25.5 (3.0-16.0), AMA neg, ALKM neg.

Ultrasound:
Q 1

Possible diagnoses?
A. DILI
B. AIH
C. IRIS
D. Gallstones
E. Fibrosing cholestatic hepatitis
ANSWER

• A B C all possible
Fibrosing cholestatic hepatitis

- Rare, severe form of HBV (also HCV)
- Often fulminant course
- Cholestasis and rapid progression to failure
- Associated with severe immunosuppression
- Features: Severe cholestasis, ground glass appearance, ballooning hepatocytes, fibrosis extending from portal tracts, scant inflammatory infiltrate
- Treatment: response to nucleoside analogues
DILI

- Incidence of liver elevation around 5-10% in first 12 weeks
- Risks: HCV, advanced liver fibrosis, male sex

- SA setting: HBV and TB medication

1. AIDS 2013:27(7)1187
2. AIDS.2007: 21(10):1301-1308

Proportion with hepatotoxicity

Time on ART (months)

- HBsAg(-) / TB med(-)
- HBsAg(+) / TB med(-)
- HBsAg(-) / TB med(+)
- HBsAg(+) / TB med(+)

DOI: 10.1097/QAD.0b013e32814e6b08
Course...

- Liver tests worsened with T Bili rising to 286, ALT 447
- No evidence of progression clinically
What would you do next?

A. Continue to watch her for 7 days
B. Stop all her ARVs and monitor LFTs
C. Perform a liver biopsy
D. Re-check her HBV Viral load
Q2

- Answer C
Case 1

- She has a diagnostic procedure performed
Liver biopsy
Liver biopsy report:

- Moderate portal inflammation, mostly lymphocytes, occasional plasma cells. Eosinophils present.
- Moderate interface hepatitis.
- Bridging necrosis.
- Bridging fibrosis, regenerating nodules.
- Ballooning hepatocytes, rosettes.
- Mild cholestasis.
## AIH Simplified Scoring Criteria 2008

*Hepatology* 2008;48:169-176

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA</td>
<td>1:40</td>
<td>1</td>
</tr>
<tr>
<td>ANA or SMA or LKM</td>
<td>1:80</td>
<td></td>
</tr>
<tr>
<td>or SLA</td>
<td>Positive</td>
<td>2</td>
</tr>
<tr>
<td>IgG</td>
<td>Upper normal limit</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.10 times normal limit</td>
<td>2</td>
</tr>
<tr>
<td>Liver histology&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Compatible with AIH</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Typical AIH</td>
<td>2</td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Definite H: ≥7</td>
<td>Probable AIH: ≥6</td>
<td></td>
</tr>
</tbody>
</table>
Our patient...

- ANA positive at 1:160 = 2 points
- IgG is 25.5 (>1.104ULN) = 2 point
- Histology is typical = 2 points
- No viral hepatitis = 0 points

Total is 6 points: Probable AIH
<table>
<thead>
<tr>
<th>Characteristic autoantibodies</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antinuclear antibody (20% of patients are negative for all conventional autoantibodies)</td>
<td>Anti-liver-kidney microsomal antibody type 1 (rarely detected in North America)*</td>
</tr>
<tr>
<td></td>
<td>Anti-smooth-muscle antibody</td>
<td>Anti-liver-cytosol antibody type 1 antibody</td>
</tr>
<tr>
<td></td>
<td>Anti-actin antibody</td>
<td>Anti-liver-kidney microsomal antibody type 3</td>
</tr>
<tr>
<td></td>
<td>Anti-soluble-liver-antigen or anti-liver-pancreas-antigen antibodies</td>
<td></td>
</tr>
<tr>
<td>Geographical variation</td>
<td>Worldwide</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>All ages</td>
<td>Usually childhood and young adulthood</td>
</tr>
<tr>
<td>Female-to-male ratio</td>
<td>4:1</td>
<td>10:1</td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td>Variable</td>
<td>Generally severe</td>
</tr>
<tr>
<td>Histopathological features at presentation</td>
<td>Broad range: mild disease to cirrhosis</td>
<td>Generally advanced: inflammation and cirrhosis common</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Relapse after drug withdrawal</td>
<td>Variable</td>
<td>Common</td>
</tr>
<tr>
<td>Need for long-term maintenance</td>
<td>Variable</td>
<td>About 100%</td>
</tr>
</tbody>
</table>

*Although immunofluorescence is the most appropriate method to measure conventional autoantibodies in autoimmune hepatitis, many laboratories (especially those in the USA) are increasingly using ELISA-based methods to detect these antibody profiles. The profiles of anti-liver-kidney microsomal antibody type 1 can be erroneously reported as detectable antimitochondrial antibodies.*

**Table 1:** Classification of autoimmune hepatitis on the basis of autoantibody profiles
<table>
<thead>
<tr>
<th>Standard treatment</th>
<th>Alternative treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td></td>
</tr>
<tr>
<td>Prednis(ol)one 40–60 mg/day (taper to 10 mg/day in 6–12 weeks); add azathioprine† when aspartate aminotransferase decreased to 2–3 times normal range</td>
<td>Alternative 1: mycophenolate mofetil 1g twice a day; ciclosporin to achieve trough concentrations of the drugs of 150–250 ng/mL</td>
</tr>
<tr>
<td>Alternative 1: prednis(ol)one 20 mg/day; azathioprine† 1 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Alternative 2 (for patients without cirrhosis):</td>
<td></td>
</tr>
<tr>
<td>budesonide 9 mg/day (taper over 6–18 weeks); azathioprine 1 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance of remission</strong></td>
<td></td>
</tr>
<tr>
<td>Increase azathioprine to 2 mg/kg per day; steroid withdrawal during 3 months</td>
<td>Tacrolimus to achieve trough concentrations of the drugs of 6–10 ng/mL</td>
</tr>
<tr>
<td>Alternative: steroid monotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Cholestatic features</strong></td>
<td></td>
</tr>
<tr>
<td>Addition of 12–15 mg/kg per day ursodeoxycholic acid in divided doses</td>
<td>Cyclophosphamide, methotrexate, sirolimus</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td></td>
</tr>
<tr>
<td>Prednis(ol)one 40–60 mg/day (slow taper to 15 mg/day); institute azathioprine when not previously used</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment failure of fulminant disease</strong></td>
<td></td>
</tr>
<tr>
<td>Orthotopic liver transplantation</td>
<td></td>
</tr>
</tbody>
</table>

*When standard treatment fails or when there are contraindications to steroids (severe osteoporosis, psychosis, morbid obesity, and severe diabetes mellitus). †Check TPMT genotype: if homozygous, no azathioprine; if heterozygous, begin azathioprine at dose of 0.5 mg/kg/day and monitor white cell count every week.

**Table 4: Treatment options**
Course...

- Patient was started on ursodeoxycholic acid and prednisone.
- Symptoms improved
- LFTs improved
- Continued on ARVs.
# LFT results

<table>
<thead>
<tr>
<th></th>
<th>15/1/14</th>
<th>9/4/14</th>
<th>14/5/14</th>
<th>28/5/14</th>
<th>11/6/14</th>
<th>9/7/14</th>
<th>6/8/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Bili</td>
<td>72</td>
<td>286</td>
<td></td>
<td>215</td>
<td>150</td>
<td>70</td>
<td>44</td>
</tr>
<tr>
<td>ALP</td>
<td>1198</td>
<td>1075</td>
<td>1013</td>
<td>571</td>
<td>413</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>3369</td>
<td>2371</td>
<td></td>
<td>1189</td>
<td>1322</td>
<td>1021</td>
<td>1281</td>
</tr>
<tr>
<td>ALT</td>
<td>249</td>
<td>447</td>
<td>266</td>
<td>171</td>
<td>192</td>
<td>106</td>
<td>119</td>
</tr>
</tbody>
</table>
What was the correct diagnosis?

- Autoimmune hepatitis on background of chronic HBV infection and past ETOH misuse?
- Role of DILI?
- Role or IRIS?
“What is the student but a lover courting a fickle mistress who ever eludes his grasp?”

William Osler
AIH from IRIS

- IRIS has been reported to have led to sarcoidosis, autoimmune thyroid disease and autoimmune arthritis.


- Bx: Hepatitis, bridging necrosis. Predominant lymphocytes. Also plasma cells and few eosinophils.

- Score: Definite AIH. Responded to prednisone.

- ARVs restarted without event.

_De novo autoimmune hepatitis during Immune reconstitution._ Clin Infect Dis 2008;46:e12-14
Causes of liver disease in patients with HIV infection

Non-HIV related liver disease
THM

- Differential can be broad in jaundiced patient

- Multidisciplinary input key

- Think about HBV (and HCV and HEV!)
Thank you
Acknowledgements

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