Acute Hepatitis in a Patient with NASH and Elevation of CMV-IgM
Uta Drebber, MD

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Dr. Uta Drebber declares she has no conflict(s) of interest to disclose.

Case history

• 49 year old Caucasian male patient
• Progressive malaise and worsening general state
• Nausea, vomiting, diarrhea, coughing
• Admission to hospital due to chest pain

Past medical history and medication

• Adipositas (BMI 38)
• Type 2 diabetes mellitus (HbA1c 8.6 %)
• Hypertension (171/92)
• Obstructive sleep apnea
• Elevated transaminases suspicious of NASH
• Oral antidiabetic, Insulin
• ACE inhibitor, beta receptor blocker, Thiazide diuretic
• Thyroxine
• Proton pump inhibitor

Laboratory values on admission

• Normal Troponin and CK-MB
• AST 440 U/l
• ALT 412 U/l
• gGT 785 U/l
• LDH 458 U/l
• CRP 3.9 mg/dl
• AP normal
• Bili normal
• Renal function normal

• Ferritin 1902.7 ug/l
• Hepatitis A, B, C negative
• CMV-IgG-EIA 1:32000 Titer (1:230)
• CMV-IgM-EIA 2.5 Index (1-2)
• EBV-VCA-IgG 306 Elmi neg <20
• EBV-VCA-IgM 11 Elmi neg <20
Physical examination

- Normal vital signs
- Slight sceral icterus
- Protuberant abdomen, non-tender

Ultrasound

Further anamnestic information

- Carrier at the federal armed forces
- No significant alcohol consumption
- No history of traveling into foreign countries
- Married, his wife without symptoms

Time course of AST and ALT

- Admission to hospital
- Liver biopsy
- GOT
- GPT
- AST
- ALT

Liver biopsy images
Pathological diagnosis

- Non alcoholic steatohepatitis (NASH)

- Marked lobular and portal mixed inflammation with spotty necrosis and apoptotic bodies raises the question of a separate disease process especially acute viral hepatitis

- No typical signs of CMV hepatitis, negative CMV immunohistochemistry

Additional diagnostic findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis E (Genotype 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis E- IgG</td>
<td>neg</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Hepatitis E- IgM</td>
<td>pos</td>
<td>&gt;24</td>
</tr>
<tr>
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<td>neg</td>
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</table>

Hepatitis E RNA in stool: positive

HEV real-time PCR of liver biopsy

Time course of AST and ALT

Admission to hospital: 12.04.2016
AST: 453 U/L
ALT: 670 U/L

Final diagnosis

Autochthonous acute hepatitis E with pre-existing NASH and false-positive serology against CMV

Root of infection: undercooked meet from wild pig

Wife: asymptomatic infection

Autochthonous hepatitis E: epidemiology

<table>
<thead>
<tr>
<th>Country</th>
<th>HEV IgG seroprevalence: %</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>27.0</td>
</tr>
<tr>
<td>France (Midi-Pyrennes)</td>
<td>52.5</td>
</tr>
<tr>
<td>Germany</td>
<td>29.5</td>
</tr>
<tr>
<td>England</td>
<td>12</td>
</tr>
<tr>
<td>USA</td>
<td>16</td>
</tr>
<tr>
<td>Australia</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Serological antibody response to HEV

- www.cdc.gov/hepatitis/index.htm

Serological cross reactivity for HEV, HAV, CMV, EBV
- Polyclonal stimulation of memory B-cell clones and immunological cross reactivity
- False reactivity to anti-HEV-IgM in Herpesvirus infections like EBV, CMV
- False reactivity to anti-HEV-IgM in HAV-hepatitis
- False reactivity to anti-EBV-IgM or anti-CMV-IgM in HEV-hepatitis


CMV hepatitis
- CMV immunohistochemistry

EBV hepatitis
- EBER-ISH

Acute hepatitis A

Pathology of acute autochthonous hepatitis E
- Acute viral hepatitis with lobular disarray and reticulin framework distortion (Theise, Dalton)
- Portal inflammation with polymorphs and lymphocytes (Peron 2007)
- Polymorphs in the periphery and interphase and lymphocytes centrally in the portal tracts (Malcom 2007)
- Lymphocytic destructive cholangitis (Wendum 2005)
- Acute hepatitis, spotty necrosis, portal infiltrate, polymorphs and lymphocytes, cholangitis (Drebber 2013)
Differential diagnosis for hepatitis E

- **Differential diagnosis**
  - Causes of acute and a serum ALT < 300 IU/L:
    - Drug-induced liver injury
    - Liver tumors
    - Autoimmune hepatitis
    - Acute HEV infection
    - Hepatitis A
    - Hepatitis B
    - Hepatitis C
    - Chronic hepatitis
  - Causes of an ALT 300–1000 IU/L:
    - HBV (chronic hepatitis B virus infection)
    - HCC (hepatocellular carcinoma)
    - Cholestasis
    - Cholangitis
    - Autoimmune liver disease
    - Primary biliary cirrhosis
    - Alcoholic liver disease
    - Fatty liver
    - Drug-induced liver injury
    - Chronic hepatitis C
    - Chronic hepatitis A
    - Hepatitis B
  - Hepatitis E virus: time to change the textbooks.
    (Dalton et al. Dig Dis 2016)

Concurrence of NASH with viral acute hepatitis

- **NASH**
  - Steatosis
  - Mild mixed lobular acute and chronic inflammation
  - Ballooning degeneration
  - Intrahepatic sinusoidal fibrosis
  - Mallory-Denk bodies
  - Glycogenated nuclei
  - Lipogranulomas
  - Mild portal inflammation
  - Portal fibrosis

- **Classic acute hepatitis**
  - Inflammatory cell infiltration
  - Apoptosis
  - Spotty/confluent necrosis
  - Macrophage activity
  - Liver cell damage
  - Liver cell regeneration
  - Portal tract inflammation
  - Bile duct damage
  - Cholestasis

Summary

- Autochthonous hepatitis E is an important differential diagnosis of acute and chronic hepatitis (for clinicians and pathologists)
- Serological testing should be performed routinely in patients with acute hepatitis
- Cross reactivity among HEV, HAV, CMV, EBV can be misleading
- Acute hepatitis E can concur with other liver diseases
- Pattern of viral hepatitis with mixed infiltrate, cholangitis

Hepatitis E virus: time to change the textbooks.
(Dalton et al. Dig Dis 2016)

Suggested testing algorithm for HEV

- **Suggested testing algorithm for HEV**
  - Immunocompetent
    - ALT > 300 IU/L
    - TdT
    - Decompensated chronic liver disease
    - Guillain-Barré syndrome
    - Neurologic amyotrophy
    - Patients with unexplained acute neurology and a raised ALT
  - Immunocompromised (developed countries)
    - As above
    - Persistent abnormal ALT
    - Yearly PCR

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