Liver Disease That Presents with Jaundice (PBC, Alcohol and Drugs): Diagnosis and Patient Management

Emma Pham, PA-C
Case: JL (jaundiced lady)

• A 72 year old woman presents to her primary care provider with complaints of fatigue and generalized pruritus.

• She was treated for a urinary tract infection with an antibiotic she cannot recall 6 weeks prior

• Medications: none

• PMH/PSH: no known medical problems, cholecystectomy at age 50
Case: JL (jaundiced lady)

- Social Hx: drinks 1-2 glasses of wine 4-5 days per week; no travel, no exposures
- Exam shows thin female, jaundiced, normal musculature, no encephalopathy, no organomegaly, ascites or edema
- Ultrasound of abdomen shows no abnormalities
- Labs: CBC normal, T bilirubin 12 (direct 10), AST 314, ALT 428, AP 158, GGT 210
- INR 1.2, creatinine 0.9
Issues to Consider for this Jaundiced Lady

• Alcohol
• Medication
• Intrinsic Liver Disease
Alcohol is a Global Problem

- Disproportionately affects low SES/marginalized populations
- Up to 48% of cirrhosis-related deaths in US

Rehm Lancet 2009.
Alcohol is a Major Burden

- 3.8% of **ALL** deaths worldwide in 2004
  - 6.3% for men vs. 1.1% for women
  - 9.5 per 10,000 men vs 2.1 per 10,000 women in Africa

Only 15-20% of chronic alcoholics develop chronic liver disease. Genetics clearly important but poorly understood.

How Many of These Guys Will Develop Cirrhosis?
Clinical Features Acute Alcoholic Hepatitis

• History
  • Alcohol intake – usually binge, usually honest (not always)
  • Fever
  • Weight loss – malnutrition

• Exam
  • Toxic looking, fever, tachycardia
  • Tender hepatomegaly +/- bruit
  • Signs of chronic liver disease & malnutrition – often severe

Acute alcoholic hepatitis vs decompensated alcoholic cirrhosis? No reliable indicator aside from recent alcohol intake.
Lab Features

• Liver Tests
  • AST:ALT>2:1
    • Rarely above 300 (never above 500 IU/L)
    • AST increased due to mitochondrial damage
  • GGT +/- ALP elevation – may appear very cholestatic
  • Bilirubin & INR increased, albumin depressed

• CBC
  • WBC elevation with PMNs → but may be infection
  • Low platelets → direct bone marrow suppression vs portal hypertension
  • Low hemoglobin → nutritional deficiency, bleeding

• Creatinine
  • Predictor of outcome – very important
Discriminant Function

Maddrey’s (modified) discriminant function (mDF)

\[
\text{mDF} \geq 32
\]

With encephalopathy 45% mortality
Without encephalopathy 35% mortality

More recent data \(\rightarrow\) up to 100% survival <32 & 34% 28d mortality untreated cohorts

Treatment
Resuscitation

• Sick patients!

• Address other issues:
  • Ascites → tap to r/o SBP
  • Infection → low threshold for antibiotics
  • Renal function → make sure fluid replete, no NSAIDs, careful with diuretics and contrast dye, albumin
  • Encephalopathy → lactulose
  • Alcohol withdrawal → benzodiazepines
  • Nutrition is critically important
    • Vitamins B complex (Wernicke’s)
    • Protein
Effective Therapies?

• Pentoxyfilline of no benefit

• Prednisone likely has a modest EARLY benefit but no long-term benefit

• ABSTINENCE is key (and the only thing that matters)
Importance of Drug-Induced Liver Injury (DILI)

• The liver is a major target organ for serious adverse effects of drugs
• Major cause of fulminant hepatic failure
• Drugs are a frequent cause of undiagnosed liver disease
• DILI is most common reason for post marketing withdrawal of medications
Classification of DILI

• Direct (intrinsic) hepatotoxicity
  • Usually dose-related
  • Short interval between ingestion and evidence of toxicity
  • Reproducible in animal models

• Idiosyncratic hepatotoxicity
  • Not always dose-related
  • Usually not reproducible in animal models
  • Host factors play important role in risk
Direct Hepatotoxicity: Acute Necrosis

• Elevation in ALT and AST, even up to 1000s
• Elevated bilirubin and INR indicate severity
• Examples
  • Acetaminophen
  • Cocaine
  • Niacin
  • Ecstasy
  • Some chemotherapeutic agents
  • IV amiodarone
Idiosyncratic Drug Reactions

• Metabolic idiosyncrasy
  • Unusual metabolism of a drug leads to injury

• Immunologic idiosyncrasy
  • The host immune response “sees” the drug as a foreign antigen and this leads to reaction
Clinical Spectrum of Idiosyncratic DILI

• Hepatocellular injury
  • ALT and AST are primarily elevated

• Intrahepatic cholestasis
  • Alk phos is primarily elevated

• Mixed cholestatic/hepatocellular injury
  • ALT/AST & Alk phos are both elevated
Top 10 Causes of Idiosyncratic DILI

1. Amoxicillin-clavulanate
2. Isoniazid*
3. Nitrofurantoin*
4. TMP-SMX
5. Minocycline
6. Cefazolin
7. Azithromycin*
8. Ciprofloxacin*
9. Diclofenac*
10. Levofloxacin*

• *If jaundiced, fatality rate >10%
• All are older drugs approved before 2000
Newer Drugs in Top 50 DILI Cases

- Duloxetine
- Rosuvastatin
- Telithromycin
- Imatinib
- Atomoxetine
- Oxaliplatin
- Flavocoxid
Herbal and Dietary Supplements

• 16% of all cases of hepatotoxicity are OTC
• Anabolic steroids—bland cholestasis
• Many cause acute necrosis/inflammation
  • Herbalife, Hydroxycut
Primary Biliary Cholangitis (PBC)
PBC is a Chronic, Progressive Autoimmune Disease

- Factors possibly associated with onset and perpetuation of bile-duct injury in PBC

PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

# PBC Phenotype

<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th>• Usually &gt;45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>• Female &gt; Male (9:1)</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>• AMA in ~95%; disease-specific ANA in ~30%–50%; ASMA may be present</td>
</tr>
<tr>
<td><strong>Immunoglobulin</strong></td>
<td>• IgM typically elevated</td>
</tr>
<tr>
<td><strong>MRCP</strong></td>
<td>• Normal</td>
</tr>
<tr>
<td><strong>Liver Histology</strong></td>
<td>• Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present</td>
</tr>
<tr>
<td><strong>Coexisting IBD</strong></td>
<td>• Not typical</td>
</tr>
</tbody>
</table>

Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cirrhosis.

## Concomitant Autoimmune Disease in Women with PBC

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s syndrome</td>
<td>7-34</td>
</tr>
<tr>
<td>Raynaud’s syndrome</td>
<td>9-13</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>11-13</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3-8</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>6</td>
</tr>
<tr>
<td>Scleroderma or CREST*</td>
<td>1-2</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>1</td>
</tr>
<tr>
<td>Any autoimmune disease</td>
<td>33-55</td>
</tr>
</tbody>
</table>

*CREST (calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia)

Diagnosis of PBC: Is Biopsy Needed?

• If:
  • Increased AMA
  • ALP >1.5x ULN
  • AST <5x ULN

• Then:
  • Positive predictive value for PBC >98%
    • Sensitivity 80%, specificity 92%

Pruritus Is Common Among PBC Patients

- Prevalence reported as high as 69%\(^1\)
- Unknown etiology\(^{1,2}\)
  - Bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid are suspected pruritogens\(^2\)
- Diurnal variation – most intense itch in the late evening\(^2\)
- Localization reported at limbs – soles and palms\(^2\)
- Exacerbated by pregnancy or contact with wool/heat\(^3\)

First Line: Ursodeoxycholic Acid (UDCA)

• Orally administered, naturally occurring, hydrophilic secondary bile acid
• Dose: 13-15 mg/kg/day
• Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months

Second Line: Obeticholic Acid (OCA)

- Approved in 2016 for patients with an inadequate response to UDCA or cannot tolerate it
- Farnesoid X receptor (FXR) agonist
- Oral medication taken in combination with UDCA or by itself in patients who cannot tolerate UDCA
- Approved based on a study showing a reduction in ALP
- No data available showing improvement in symptoms or reduction of long-term morbidity and mortality
# OCA Adverse Events in Clinical Trials


<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=73)</th>
<th>OCA 5-10 mg (N=70)</th>
<th>OCA 10 mg (N=73)</th>
<th>Open Label (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>28 (38)</td>
<td>39 (56)</td>
<td>50 (68)</td>
<td>138 (72)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (18)</td>
<td>17 (24)</td>
<td>13 (18)</td>
<td>45 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (18)</td>
<td>12 (17)</td>
<td>6 (8)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (14)</td>
<td>11 (16)</td>
<td>17 (23)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (12)</td>
<td>4 (6)</td>
<td>8 (11)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>SAE</td>
<td>3 (4)</td>
<td>11 (16)</td>
<td>8 (11)</td>
<td>27 (14)</td>
</tr>
</tbody>
</table>
Back to Our Case: JL (jaundiced lady)

- AMA negative
- Viral serologies negative

- Liver biopsy is performed and consistent with cholestasis, moderate portal inflammation

- Call to pharmacy reveals she had taken nitrofurantoin for UTI
Outcome of JL (jaundiced lady)

• Resolved slowly over 2 months
• Avoided alcohol and other meds during that time
• Noted drug allergy in her records
Many conditions present with jaundice
Alcohol and medications/drugs are two of the more common reasons
Primary autoimmune conditions are on the rise

A thorough history, imaging and laboratory testing are essential to making the diagnosis
Roundtable Discussion/Q&A

Dr. Alkhouri and Emma Pham
Lunch/Non-Accredited Symposium
Lunch/Non-Accredited Symposium
Box lunches in foyer