Patient Identification

The patient is a 19-year-old female of mixed European Ancestry.

Current Illness Progression

2.5 weeks prior to admission
Patient began experiencing malaise, vomiting and upper respiratory symptoms which resolved in 3 days.

1 week prior to admission
Development of pruritus, dark urine and darkening of her skin.

4 days prior to admission
Patient began to experience a headache.

3 days prior to admission
Increasing discoloration of the eyes and skin, malaise decreased appetite and weight loss of 6.6 lb.

2 days prior to admission
Abdominal pain began.

Day of admission
Patient was admitted to the hospital due to increasing pruritus and nausea.
Symptomatology

Primary symptoms present upon admission to hospital: nausea, jaundice, and pruritus

Nausea - a feeling of sickness with an inclination to vomit

Jaundice - yellowing of the skin or whites of the eyes, arising from excess bilirubin

Pruritus - clinical term for itchy skin

Question 1:

What is bilirubin?

a. A yellow pigment created by breakdown of dead red blood cells
b. A yellow pigment created by breakdown of dead white blood cells
c. A yellow byproduct from the liver’s role in chemical detoxification and drug metabolism
d. A yellow byproduct from the digestion of fat in the gallbladder
e. A yellow pigment produced by the skin to protect it from UV rays
Past Medical History

- Three months prior, the patient gave birth after full term pregnancy with no complications
- History of migraines.
- Possible family history of alcoholic liver disease
  - Paternal grandmother dying of Laënnec's cirrhosis.
Social history

- Patient reports smoking cigarettes
- Rarely consumes alcohol
- No use of intravenous drugs or eating wild mushrooms.
- Patient lived with her child and boyfriend in a rural area and stopped working shortly after pregnancy
- Had not recently travelled out of the New England area.
Allergies/Medications

- Three doses of oxycodone-acetaminophen received from a friend
- Pseudoephedrine
- Tablets containing a mix of aspirin, caffeine and acetaminophen
- The patient has no allergies.
Vitals

3 Days pre-admission-
Vital signs normal

On admission-
Awake, alert, and oriented.

Blood pressure: 143/83 mm Hg

Other vital signs were normal

https://tinyurl.com/y9xmgfv4
Physical Findings

The conjunctivae and skin were markedly icteric (synonymous with having jaundice); the remainder of the examination was normal.

**Question 2 (A)**

How are the liver and gallbladder related?

- a. The common hepatic duct joins with the cystic duct of the gallbladder, forming the common bile duct.
- b. The common hepatic duct is attached directly to the gallbladder.
- c. They are connected by the hepatic vein.
- d. The liver and gallbladder are not connected.
- e. The mucosal duct goes through the duodenum and connects with the cystic duct of the gallbladder, forming the common bile duct.

[https://lifespa.com/gallbladder-health-food-and-recipes/]
Labs and Radiology: Urinalysis

Dipstick test: Orange, clear urine with a pH of 6.5, a specific gravity of 1.010, 3+ bilirubin, 2+ blood
Labs and Radiology: Urinalysis

Microscopic exam:

- 20 to 50 white blood cells per high-power field
- 0 to 2 red blood cells per high-power field
Question 3: Blood Composition

Which of the following correctly identifies the component percentages of blood volume in a healthy adult human?

a. 20% plasma and 80% erythrocytes
b. 55% plasma and 45% erythrocytes
c. 80% plasma and 20% erythrocytes
d. 45% plasma and 55% erythrocytes
e. 70% plasma and 30% erythrocytes
## Labs and Radiology: Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults</th>
<th>3 Days before Admission, Other Hospital</th>
<th>1 Day before Admission, Other Hospital</th>
<th>On Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated partial-thromboplastin time (sec)</td>
<td>21.0–33.0</td>
<td>29 (ref 24.0–31.6)</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>10.8–13.4</td>
<td>12.6 (ref 8.9–10.6)</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0–1.0</td>
<td>11.6</td>
<td>15.6</td>
<td>16.8</td>
</tr>
<tr>
<td>Direct</td>
<td>0.0–0.4</td>
<td></td>
<td></td>
<td>12.0</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>9–32</td>
<td>869</td>
<td>829</td>
<td>1035</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>7–30</td>
<td>908</td>
<td>931</td>
<td>1176</td>
</tr>
<tr>
<td>Salicylate (mg/dl)</td>
<td></td>
<td>7 (ref 10–25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody to hepatitis B surface antigen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus surface antigen</td>
<td>Nonreactive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>Negative at 1:40 and 1:160 dilution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimitochondrial antibodies</td>
<td>Negative at 1:20 dilution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-smooth-muscle antibodies</td>
<td>Negative at 1:20 dilution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies to liver–kidney microsomes (U)</td>
<td>&lt;20.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ref denotes reference range. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for salicylate to millimoles per liter, multiply by 0.07240.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
Question 4 (Dilution Factors):
Which of these results most strongly indicates that antibodies associated with smooth muscle have been upregulated?

<table>
<thead>
<tr>
<th>Table 1.1 Laboratory Data</th>
<th>Reference Range</th>
<th>On Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Anti-smooth-muscle antibodies</td>
<td>Negative at 1:40 and 1:160 dilution</td>
<td>Negative at 1:40 dilution, Positive at 1:160 dilution</td>
</tr>
<tr>
<td>B. Anti-smooth-muscle antibodies</td>
<td>Negative at 1:40 and 1:160 dilution</td>
<td>Negative at 1:20 dilution, Positive at 1:80 dilution</td>
</tr>
<tr>
<td>C. Anti-smooth-muscle antibodies</td>
<td>Negative at 1:40 and 1:160 dilution</td>
<td>Positive at 1:20 dilution, Negative at 1:160 dilution</td>
</tr>
<tr>
<td>D. Anti-smooth-muscle antibodies</td>
<td>Negative at 1:40 and 1:160 dilution</td>
<td>Positive at 1:40 dilution, Negative at 1:160 dilution</td>
</tr>
<tr>
<td>E. Anti-smooth-muscle antibodies</td>
<td>Negative at 1:40 and 1:160 dilution</td>
<td>Positive 1:10 dilution Negative 1:80 dilution</td>
</tr>
</tbody>
</table>
Question 5: Bilirubin Production (Biochemistry)

Which of the following is a likely cause of high serum bilirubin levels?

a. Downregulation of biliverdin reductase
b. Upregulation of bilirubin oxidase
c. Increase in hemolysis
d. Decrease in erythropoiesis
e. All of the above
Labs and Radiology: Figure 1
Abdominal Ultrasonogram

A. Cholelithiasis

B. Thickening of the gallbladder wall (arrows) to 0.7 cm (normal, <0.4 cm)

C. Shows an apparently normal hepatic parenchyma
   a. No evidence of biliary obstruction
Question 6: Ultrasonogram

How is an image obtained during an ultrasonogram?

A. X-rays beams are passed through the body as it moves through the scanner at various angles to create cross-sectional images of the body
B. High energy sound waves are bounced off internal organs and tissues to make echoes which form an image of internal structures
C. A strong magnetic field and radio frequency pulses are used to produce the image of internal body structures
D. Use of electromagnetic radiation in conjunction with high energy sound waves creates an image of internal structures
E. None of the above
Labs and Radiology: Figure 2
Liver-Biopsy Specimen

- **Panel A**
  - H&E stain showing the liver, which is normally organized into hexagonal plates called lobules, is no longer properly organized
  - Panlobular hepatitis (inflammation of the entirety of each lobule)
  - Hepatocyte necrosis

- **Panel B**
  - H&E Stain showing mononuclear cells (lymphocytes and monocytes) and plasma cells accumulating at sites of inflammation

- **Panel C**
  - Periodic acid-Schiff staining shows ceroid laden macrophages (accumulation of a yellow-brown pigment in cells associated with diseased states)

- **Panel D**
  - Trichrome staining reveals no bridging fibrosis or cirrhosis (later stages in liver disease)
Question 7: Visualization Techniques

Which of the following correctly identifies the function and techniques?

I. Ultra sonography - use of low frequency sound waves to produce an image by analyzing the pattern of sound waves bouncing off of tissue surfaces
II. Biopsy - extraction of sample cells or tissues for examination
III. H&E Staining - Counterstain that helps differentiate between the cytoplasm and nuclei.

a. I. and II.
b. II. and III.
c. I. and III.
d. I., II., and III.
e. None of the above
What is the diagnosis?
Differential Diagnosis

- Chronic Viral Hepatitis
- Drug induced liver disease
- Autoimmune hepatitis
- Wilson’s Disease
Viral Hepatitis

- An infection that causes liver swelling and damage
- Viral hepatitis accounts for more than 50% cases of acute hepatitis in the US.
- Could possibly be caused by hepatitis A, B or C or be a hepatitis-like illness caused by Epstein-Barr virus or Cytomegalovirus infection.
- Symptoms: fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, grey-colored stools, joint pain, and jaundice.
Drug and Toxin Induced Hepatitis

- Can be caused by alcohol, drugs, or nutritional supplements
- Acetaminophen is the most common dose-dependent cause of hepatotoxicity
  - Usually develops after overdose or in habitual drinkers who regularly take acetaminophen
- Patients present with nausea, vomiting, fatigue, lack of appetite, and dark urine
Wilson’s Disease

- A rare, genetic disorder that causes accumulation of copper throughout vital organs, including the liver.
- Symptoms: Fatigue, lack of appetite or abdominal pain, jaundice, golden-brown eye discoloration, fluid buildup in the legs or abdomen, problems with speech, swallowing or physical coordination, uncontrolled movements or muscle stiffness

https://www.nature.com/articles/s41572-018-0018-3
Autoimmune Hepatitis (AIH)

- Disorder of unknown cause characterized by inflammation of the liver, hypergammaglobulinemia, and the presence of autoantibodies
  - Autoantibody - antibody produced by the immune system that is directed against one or more of an individual's own proteins
- Often presents with nonspecific symptoms of fatigue, anorexia, nausea, abdominal pain, jaundice, arthralgia, and epistaxis
- No specific diagnostic test - must rule out other common liver diseases
  - Scoring system for diagnosis based on serum IgG levels, presence & level of autoimmune antibodies, the absence of viral markers, histological features on liver biopsy
- Type 1 or type 2 characterized on the basis of autoantibodies
  - Anti-nuclear and/or anti-smooth muscle antibodies being the markers of type 1 AIH
  - Anti-liver kidney microsomal antibody being the markers of type 2 AIH
Further considerations

- Acute biliary obstruction
- Acute cholecystitis
- Acute Hepatic vein thrombosis
  - Because of recent pregnancy
- Ischemic Hepatitis
- Celiac Disease
- Pregnancy Related Liver disease

https://www.intechopen.com/books/acute-pancreatitis/acute-biliary-pancreatitis
What is the diagnosis?
Viral Hepatitis Test Results

- Patient tested negative for the IgM antibody for hepatitis A virus, negative for the hepatitis B surface antigen and negative for anti-HCV antibodies.
- Patient’s serum was absent of EBV DNA or CMV antigenemia (the condition of having an antigen present in the blood).

[https://www.healthline.com/health/antinuclear-antibody-panel](https://www.healthline.com/health/antinuclear-antibody-panel)
Drug and Toxin Induced Hepatitis Test Results

- No excessive alcohol use or ingestion of acetaminophen
- Aminotransferase levels not consistent with alcoholic hepatitis
  - Alcoholic hepatitis --> AST:ALT ratio of 2+
    - Patient AST: ALT ratio was ~1
- No exposure to drugs which may cause hepatitis on allergic basis
- No exposure to poisonous mushrooms, drugs of abuse, herbal remedies, or weight-loss aids
  - Toxicology screen on admission was negative
Wilson’s Disease Test Results

- Testing for copper levels in liver tissue can identify this disease
  - 250 µg of copper per gram of liver tissue tested or more to be indicative of the disease
- The patient tested as having 54 µg of copper per gram of tissue
- The reference range for copper tissue level is 10-35 µg per gram.

https://en.wikipedia.org/wiki/Wilson%27s_disease
Question 8-
Why do you think the patient exhibited a copper tissue level higher than normal?

a. Her recent weight loss led her body to start storing more vitamins and minerals.
b. She had Wilson’s disease.
c. The liver was not processing it properly, leading to an accumulation.
d. Copper levels are expected to increase postpartum.
e. She had increased Ca^{2+} levels causing her copper levels to rise.
What was the definite diagnosis?

Autoimmune Hepatitis
Question 9: Antibodies (Physiology)

How do humans get rid of autoantibodies?

a. By increasing the production of self antigens
b. By destroying antibodies that react to self antigens
c. By creating antibodies that react to self antigens
d. By decreasing the production of self antigens
e. By increasing the number of lymphocytes
The point system used is the standard scoring chart for diagnosing autoimmune hepatitis.

Autoantibodies - as mentioned previously, autoantibodies react with self antigens

Serum IgG level - An increase in IgG would indicate an enhanced immune response

Liver Biopsy Histology - characteristic signs of AIH previously mentioned

“I calculate a score of 7. The patient had an anti-smooth-muscle antibody titer of 1:80 (2 points), an elevated IgG level (1 point), an absence of viral hepatitis (2 points), and typical histologic findings on biopsy (2 points). This makes the diagnosis definite.”

-Lawrence S. Friedman, M.D.
### Table 3. Classification of Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic autoantibodies</td>
<td>Anti–smooth-muscle, antinuclear</td>
<td>Antibodies to liver–kidney microsome type 1</td>
</tr>
<tr>
<td>Associated autoantibodies</td>
<td>Atypical pANCA; antibodies to actin asialoglycoprotein receptor, chromatin, soluble liver antigen</td>
<td>Antibodies to liver cytosol type 1, soluble liver antigen</td>
</tr>
<tr>
<td>Putative autoantigen</td>
<td>Unknown</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Age</td>
<td>Infants to elderly</td>
<td>Children (2 to 14 yr of age)†</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Patients with concurrent immune diseases (%)</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Typical concurrent autoimmune diseases</td>
<td>Autoimmune thyroiditis, Graves’ disease, ulcerative colitis</td>
<td>Autoimmune thyroiditis, vitiligo type 1, diabetes mellitus, APECED</td>
</tr>
<tr>
<td>Organ-specific antibodies (%)</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Elevated immunoglobulins</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Glucocorticoid-responsive</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

*Data are from Czaja.*

APECED denotes autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, CYP2D6 cytochrome P-450 2D6, and pANCA perinuclear antineutrophil cytoplasmic antibodies.

†In Germany and France, 20% of adult patients with autoimmune hepatitis have type 2; it is uncommon in adults in the United States.
Question 10: Endocrinology

Which of the following is most likely a cause for autoimmune hepatitis?

a. Genetic mutation encoding MHC class II receptors in a hepatocyte

b. Infection of a hepatocyte by Hepatovirus A

c. Excessive, prolonged intake of alcohol resulting in a cirrhotic liver

d. Increased production of lymphocytes after infection by Human papillomavirus (HPV)

e. Chronic and extensive bacterial infection of hepatocytes
Treatment Progression

- Following biopsy on day 1 patient admitted to medical service
  - Abdominal pain developed w/ systolic blood pressure of 70 mmHg with bradycardia
- CT Scan revealed fluid in abdomen
  - Hematocrit 22% and patient received 2 units of packed red cells
- Taken emergently for embolization of an actively bleeding branch of the right hepatic artery
Treatment Regimen

- Hospital day 1 (post biopsy results): Treatment with 60 mg prednisone daily
- Hospital day 3: prednisone reduced to 40 mg and patient discharged
- 10 days post discharge: 50 mg of azathioprine daily, with tapering of prednisone to 10 mg daily
- 4 mo. post discharge: Liver function test normal; azathioprine increased to goal dose of 2-2.5 mg per kg body weight and prednisone discontinued
Relevance

- 75% of Americans with an autoimmune disease are women.
- On average, it takes a person with an autoimmune disease 4.6 years and 5 different doctors to receive the correct diagnosis.
- Autoimmune hepatitis can lead to cirrhosis, and those without cirrhosis have average survival rates, while those with cirrhosis increase their risk of death or requiring a liver transplantation.
Question 11: Clinical Testing

Which of the following correctly identify sensitivity and specificity?

I. Specificity is a measure of the ratio of the number of people who have the condition that are correctly identified divided by the total number of people who have the condition.

II. Sensitivity is a measure of the ratio of the number of people who do not have the condition that are correctly identified divided by the total actual number of people who do not have the condition.

III. A test with a high sensitivity has a proportionally small number of false negatives.

IV. A test with high specificity has a proportionally small number of false positives.

a. I. and II.
b. I. and IV.
c. II. and III.
d. III. and IV.
e. I., II., and III.
References


https://labtestsonline.org/tests/bilirubin

https://labtestsonline.org/tests/antinuclear-antibody-ana

https://en.wikipedia.org/wiki/Hepatitis_C_virus

https://www.cdc.gov/hepatitis/abc/index.htm
https://www.mayoclinic.org/diseases-conditions/wilsons-disease/symptoms-causes/syc-20353251
https://www.nature.com/articles/s41572-018-0018-3
https://www.healio.com/hepatology/autoimmune-cholestatic-biliary-diseases/news/online/%7Bb2dba4fe-0a9c-44e9-91ba-ca64e09e0004%7D/cirrhosis-psc-predict-
mortality-risk-in-autoimmune-hepatitis
https://www.healthline.com/health/aninuclear-antibody-panel
https://www.intechopen.com/books/acute-pancreatitis/acute-biliary-pancreatitis
https://en.wikipedia.org/wiki/Wilson%27s_disease
https://www.medicinenet.com/tylenol_liver_damage/article.htm#is_it_safe_for_me_to_take_tylenol
https://drugabuse.com/oxycodone/effects-use/

https://livertox.nlm.nih.gov/Aspirin.htm