CASE DETECTIVE Series

43-Year-Old Woman With Painful Jaundice

Case-2

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Presentation & PMH

- A **43-year-old woman** with a medical history of **stage IIIB cutaneous melanoma** previously receiving **adjuvant immunotherapy with nivolumab** **(discontinued 2 months before presentation)** presented to the emergency department with a **4-day history of nausea, vomiting, abdominal pain, and jaundice**.
- Symptoms began with **nausea and vomiting after eating a meal**. The following morning she had **dull right upper quadrant** and **periumbilical abdominal pain**.
- Her **nausea persisted**, and she had **multiple episodes of nonbloody nonbilious emesis**.
- She developed **jaundice** and had **fever** and **chills**,
- The patient also had a history of **alcohol abuse disorder**, **drinking 2 to 3 vodka drinks per day.** She took **multiple over-the-counter vitamins** and **various supplements including more than 14 different vitamins and supplements** such as **iron, boron, picolinate, chromium, milk thistle, and turmeric**, but was not taking any prescribed medications.
- She **denied acetaminophen ingestion**, or any other drugs.

Physical Examination

- **Vital signs were stable** with a temperature of 36.8°C, heart rate 80 beats/min, respiratory rate 16 breaths/min, blood pressure 110/56 mm Hg, and oxygen saturation of 98% on room air.
- W**ell-nourished woman with jaundice** in no acute distress, **alert and oriented** to person, place, time, and situation.
- She had **notable scleral icterus**.
- **Abdominal examination** was revealing of **mild diffuse tenderness most profound in the right upper quadrant** w**ithout distension, hepatosplenomegaly, or peritoneal signs**, and **no fluid shift wave**.
- She had no asterixis or spider angiomata and no peripheral edema.

Preliminary Lab tests

- **Alanine aminotransferase (ALT) 2800 U/L** (7 to 45 U/L)
- **Aspartate aminotransferase (AST) 2519 U/L** (8 to 43 U/L)
- **Total bilirubin 17.3 mg/dL** (≤1.2 mg/dL)
- **Direct bilirubin 9.5 mg/dL** (0 to 0.3 mg/dL)
- **International normalized ratio (INR) 6.9** (0.9 to 1.1)
- **Alkaline phosphatase 206 U/L (35 to 104 U/L)**
- **Lactate dehydrogenase (LDH) 569 U/L** (122 to 222 U/L)
- **Lipase 72 U/L** (12 to 61 U/L)
- **Creatinine 0.5 mg/dL** (0.59 to 1.04 mg/dL)
- **White blood cell count 7.7×10^9/L** ($(3.4 \text{ to } 9.6)\times10^9$/L)
- **Hemoglobin 12.3 g/dL** (11.6 to 15 g/dL)
- **Platelet count 131×10^9/L** ($(157 \text{ to } 371)\times10^9$/L)
- **Blood glucose 118 mg/dL** (70 to 149 mg/dL)

Preliminary Lab tests

- **Right upper quadrant ultrasound** was performed, which revealed a **thickened gallbladder wall** measuring 7 mm with **a small amount of pericholecystic fluid** and **positive sonographic Murphy sign** but no dilation of intrahepatic ducts or common bile duct.
- **Ultrasound** noted a **small hemangioma of the right hepatic lobe**.
- **Computed tomography of the abdomen and pelvis** **with intravenous (IV) contrast** was also completed without evidence of hepatic nodules or abscesses.

1. Which one of the following is the most likely etiology of this patient's presentation?

A. Cholangitis

B. Metastatic disease

C. Alcoholic hepatitis

D. Ischemic hepatitis

E. Drug toxicity

Synthesis

- Cholestasis is indicated by laboratory values with elevated direct bilirubin and alkaline phosphatase levels.
- The differential diagnosis for cholestatic jaundice is broad, and **initial evaluation** should include **a detailed history** and **physical examination** followed by **ultrasound or abdominal computed tomography imaging**
- **Patient history is crucial** and should include **all medications** and **supplements, alcohol use, and travel history**.
- **Imaging is important to assess the presence of bile duct dilation**. **If bile ducts are dilated**, proceeding with endoscopic retrograde cholangiography may be both diagnostic and therapeutic such as in cases of bile duct stones or strictures

Synthesis

- **Imaging is important** for **distinguishing between intrahepatic or extrahepatic cholestasis**.
- **Intrahepatic causes of cholestatic jaundice**
  - Drug-induced liver injury (DILI)
  - Alcoholic hepatitis
  - Viral hepatitis
  - Autoimmune hepatitis
  - Hepatic infiltration such as sarcoidosis or lymphoma
- **Extrahepatic causes**
  - Anatomical obstruction and include gallstones
  - Bile duct strictures
  - Neoplasms (most commonly pancreatic carcinoma).

Differential Dx

- **Ascending cholangitis**
  - **Charcot triad: RUQ pain, jaundice, Fever**
  - **Transaminases increase by 2-3 fold**
  - **Intrahepatic and/or extrahepatic biliary duct dilation**
- **Acalculous cholecystitis**
  - gallbladder inflammation **in the absence of gallstones**.
  - most commonly occurs in **critically ill patients with sepsis** or **prolonged absence of oral intake** with reduced gallbladder contraction.
- **Alcoholic hepatitis**
  - **jaundice, fever, tender hepatomegaly, elevated transaminase levels, and abnormal INR.**
  - **AST/ALT >2-3, Transaminase levels rarely >300 U/L**

Progress note

Over the next 20 hours after admission, the patient **became obtunded** and **responsive to painful stimuli only**.

2. Which one of the following criteria best support this patient's diagnosis of acute liver failure?

A. Acute onset of liver enzyme elevation

B. Severe liver injury, hepatic encephalopathy, and elevated INR

C. Alcohol use with liver injury but no evidence of chronic liver disease

D. Progressive jaundice

E. Acute decline in mental status

Acute Liver Failure

- **The diagnostic criteria for acute liver failure** includes
  - **Acute liver injury**
  - **Coagulopathy**
  - **Encephalopathy**
- **Progression to acute liver failure in less than 7 days: hyperacute liver failure**
- **Progression in 7 to 21 days: acute liver failure**
- **Progression in 22 to 26 days: subacute liver failure**

3. Which one of the following is the best next step in management?

A) Transfer to an intensive care unit for supportive measures
B) Initiate continuous renal replacement therapy
C) Initiate broad-spectrum antibiotics
D) Initiate fluid resuscitation
E) Initiate symptomatic control with morphine

Progress note

- The patient was tachycardic but **remained hemodynamically stable**.
- **Lactulose enemas** were initiated,
- She was **transferred to the medical intensive care unit**.
- Shortly afterward, she required **intubation for airway protection**.
- **Ultimately, treatment of acute liver failure is centered around expedient and appropriate identification of the underlying cause**.
- Results of **infectious work-up** including testing for **tick-borne diseases (Anaplasmosis, Lyme disease, ehrlichiosis and babesiosis)**, **viral hepatitis** testing, and **human immunodeficiency virus**, **Epstein-Barr virus**, **cytomegalovirus**, and **bacterial cultures** were all negative.
- **Liver biopsy** was performed and revealed **findings consistent with massive liver necrosis**.
- She was diagnosed **with immune checkpoint inhibitor (ICI)–induced hepatitis** due to **nivolumab**, a **programmed cell death protein-1 (PD-1) receptor inhibitor.**

4. Which one of the following is the most likely mechanism of this patient's acute liver injury?

A) Cytokine storm causing shock liver

B) Immune checkpoint inhibitor toxicity due to T-cell activation

C) Inhibited cytochrome P450 with increased susceptibility to alcohol toxicity

D) Adverse drug reaction inducing hepatocyte autophagy

E) Drug-induced liver injury due to direct hepatotoxicity

5. Which one of the following is the best next step in management??

A) Plasmapheresis
B) Intravenous immunoglobulins
C) Corticosteroids
D) Disease-modifying antirheumatic drugs
E) Colchicine

Synthesis

When liver enzyme levels are more than 5 times the upper limit of normal (ULN) or bilirubin levels are more than 3 times the ULN, corticosteroids with a methylprednisolone IV or oral equivalent of 1 to 2 mg/kg per day should be given with permanent discontinuation of the checkpoint inhibitor.

If the patient does not respond to high-dose corticosteroids, then a second immunosuppressive agent (ie, disease-modifying antirheumatic drugs) may be required.

Progress Note

- The patient **was not deemed to be a liver transplant candidate** owing to a history of metastatic melanoma.
- Her hospital course was further complicated by **hemorrhagic shock after liver biopsy**, and she was managed with **massive transfusion protocol**.
- **Continuous renal replacement therapy** was initiated for volume removal.
- She was treated with **high-dose steroids** but **remained persistently hypotensive**, and volume removal was not possible.
- Ultimately, her family elected for **compassionate extubation** and **transitioning her care to focus on her comfort only**.

Immune Checkpoint Inhibitor Hepatitis

- **Grade 1: AST or ALT levels 3 times the ULN**, with **total bilirubin levels 1.5 times the ULN**. **In grade 1**, **alcohol cessation** is recommended but **treatment with immunotherapy can be continued** if the patient remains asymptomatic.
- **Grade 2: AST or ALT levels 3 to 5 times the ULN**, with **total bilirubin levels 1.5 to 3 times the ULN**. **Grade 2 treatment** consists of **holding ICI and treating with oral prednisone**. If transaminase levels decrease to grade 1 or less without requiring ongoing steroids, **ICI may be reintroduced**.
- **Grade 3**: **AST or ALT levels greater than 5 times the ULN**, with **total bilirubin levels greater than 3 times the ULN**.
- **Grade 4: AST or ALT levels greater than 8 times the ULN**.
- **Treatment of grade 3 and grade 4** includes **discontinuation of ICI**, **initiation of IV corticosteroids**, and **performing a liver biopsy.**
- In patients with **grade 3 and 4 toxicity who do not respond to steroids**, **a second immunosuppressive agent may be required** and **treatment with mycophenolate should be considered.**