31-Year-Old Woman With Jaundice and Abdominal Pain

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A 31-year-old woman presented with a 3-month history of persistent jaundice. She worked as a school teacher and a student had made a comment that her eyes appeared yellow approximately 3 months before presentation. During this time, she had also noticed darkening of her skin diffusely. She had believed that these changes were secondary to indoor tanning, which she did once weekly. One week prior she developed sharp right upper quadrant abdominal pain that was worse with lying on her right side. She also began to appreciate mild lower extremity edema and darkening of her urine. Her medical history was notable for alcohol use disorder, obesity status post Roux-en-Y gastric bypass with current body mass index of 31 kg/m^2, seizure disorder, and major depressive disorder. She first began consuming alcohol at age 16 and had prolonged periods of alcohol abuse with intermittent episodes of sobriety. One year prior, she had undergone an intensive inpatient alcohol rehabilitation program. However, she admitted consuming alcohol following completion of rehabilitation, approximately "once per week." Her last drink was three days before presentation. She was taking no medications at the time of her presentation.

At presentation, the patient's vital signs were within normal limits, with heart rate 98 beats/min and blood pressure 126/77 mm Hg. Physical examination revealed right upper quadrant tenderness to light palpation without rebound tenderness or guarding. Her abdomen was distended but compressible, with tympany noted over the midline. The liver edge was palpated 2 inches below the costal margin. Scleral icterus and generalized jaundice were also noted.

Laboratory evaluation yielded the following results (reference ranges provided parenthetically): hemoglobin, 9.9 g/dL (12.0-15.5 g/dL); leukocytes, 17.1 × 10^9/L (3.5-10.5 × 10^9/L); platelets, 319 × 10^9/L (150-450 × 10^9/L); sodium, 133 mmol/L (135-145 mmol/L); potassium, 2.8 mmol/L (3.6-5.2 mmol/L); creatinine, 0.49 mg/dL (0.6-1.1 mg/dL); total bilirubin, 17.6 mg/dL (<1.2 mg/dL); direct bilirubin, 14.3 mg/dL (0.0-0.3 mg/dL); international normalized ratio (INR), 2.7 (0.9-1.1); prothrombin time (PT) 29.5 sec (9.5-13.8 sec); albumin 2.2 g/dL (3.5-5.0 g/dL); aspartate aminotransferase 207 U/L (8-43 U/L); alanine aminotransferase 22 U/L (7-45 U/L); and alkaline phosphatase 157 U/L (37-98 U/L).

1. **Which of the following is the *best initial* imaging test in this patient with right upper quadrant pain?**
   a. Computed tomography of the abdomen/pelvis with intravenous contrast
   b. Transabdominal ultrasound
   c. Endoscopic retrograde cholangiopancreatography
   d. Magnetic retrograde cholangiopancreatography
   e. Abdominal x-ray

Jaundice and right upper quadrant pain are commonly encountered presenting complaints in both the inpatient and outpatient settings. The differential for such symptoms is broad, including but not limited to biliary obstruction, excess bilirubin production, and hepatic inflammation. Given our patient's jaundice and right upper quadrant pain along with direct hyperbilirubinemia and elevated alkaline phosphatase, the suspicion for biliary obstruction was high.

Computed tomography (CT) of the abdomen/pelvis with intravenous contrast would be a reasonable initial imaging study

See end of article for correct answers to questions.

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if there was low suspicion for an obstructive process. CT imaging offers an extensive analysis of the liver, extrahepatic abdomen, and pelvis. The intravenous contrast allows for visualization and assessment of patency of vascular structures. Transabdominal ultrasound is more than 95% sensitive for gallbladder stones and is the preferred initial imaging test in patients presenting with acute right upper quadrant pain.[1] Ultrasound imaging may be limited in patients with obesity and in cases where gas overlies the bowel, making assessment of the retroperitoneum difficult. Compared to ultrasound, CT imaging is less reliable in detecting gallstones and gallbladder-wall abnormalities. Endoscopic retrograde cholangiopancreatography does not have a role in the diagnostic evaluation of a patient with jaundice but should be considered for a therapeutic intervention when a gallstone or other obstructive process is found in the biliary tree. Magnetic retrograde cholangiopancreatography has more than 90% sensitivity in detecting choledocholithiasis and permits high-quality imaging of the biliary tree. This can be a useful test in patients not likely to require therapeutic intervention.[1] The invasiveness and cost of endoscopic retrograde cholangiopancreatography and magnetic retrograde cholangiopancreatography, respectively, precludes them for being first-line imaging tests. Abdominal x-ray can be useful in cases of suspected bowel obstruction or ileus but is unlikely to provide any information regarding the biliary tract and would not be a preferred test to evaluate for right upper quadrant pain. In our patient, a transabdominal ultrasound was the best initial test as it is relatively inexpensive and can provide valuable information to help differentiate between intrahepatic and extrahepatic disease and has very high sensitivity for detecting gallstones.[2]

Our patient ultimately underwent transabdominal ultrasound, which revealed no intrahepatic or extrahepatic biliary obstruction or ascites but showed mild biliary duct wall thickening and hepatomegaly with normal hepatic vasculature.

2. **The diagnosis of acute liver failure requires severe acute liver injury and impaired synthetic function (INR >1.5) along with which *one* of the following additional features?**
   a. Portal hypertension
   b. Hepatic encephalopathy
   c. Less than 7 days of symptoms
   d. An identifiable etiology
   e. Jaundice

Identification of acute liver failure is crucial as mortality in patients not receiving liver transplant approaches 30%.[3] Whereas portal hypertension is frequently observed in patients with subacute liver failure, this is not required for diagnosis of liver failure. Hepatic encephalopathy is one of the diagnostic criteria of acute liver failure, along with an elevated INR. The timing of liver failure is very important to consider as it can help determine prognosis. Liver failure can be defined as hyperacute when it develops in less than 7 days, acute between 7 to 21 days, and subacute between 22 days and 26 weeks.[4] The determination of etiology, although not required for diagnosis, is also very important to consider in terms of prognosis and treatment. The most common etiology of liver failure in the United States is acetaminophen toxicity, whereas worldwide, viral hepatitis remains the predominant cause.[5] Jaundice is another clinical feature that is frequently seen in acute liver failure, although the presence of jaundice is also not required for diagnosis. Other common manifestations of acute liver failure include anorexia, right upper quadrant pain, fatigue, and nausea.[5]

Our patient had laboratory evidence of acute liver injury, an elevated INR, but no signs of hepatic encephalopathy.

3. **Which of the following features in our patient's history *most increases* her risk of developing alcoholic hepatitis?**
   a. Herbal supplement usage
   b. Previous cholecystectomy
   c. Previous Roux-en-Y gastric bypass
   d. Recent weight loss
   e. Female sex

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It has previously been well documented that herbal supplements can lead to hepatotoxicity.[6] In most cases, the hepatotoxicity tends to be transient; however, in other cases, chronic liver injury can result from herbal supplement use. Although there are countless herbs that have been linked to liver damage, some of the most well known culprits include black cohosh, germander, and kava.[6] Herbal supplements do not, however, impart an increased risk of alcoholic hepatitis. Similarly, cholecystectomy has not been linked with increased risk of alcoholic hepatitis. Previous bariatric surgery has been shown to drastically increase blood alcohol levels even with modest alcohol consumption and, consequently, increases risk of alcohol use disorder.[7] Furthermore, prior studies have shown that substances such as alcohol that more rapidly reach peak concentration are more addictive. This property increases the risk of alcohol-induced liver injury in patients such as ours who already have a history of alcohol use disorder. Moreover, after gastric bypass, there is decreased first pass metabolism in the stomach via alcohol dehydrogenase and gastric emptying is greatly accelerated secondary to a decreased stomach size, which leads to increased absorption of alcohol in the jejunum.[7] Weight loss does not increase risk of alcoholic hepatitis. Female sex has also not been shown to be a definitive risk factor and males represent more than 65% of patients hospitalized for alcoholic hepatitis. However, women develop alcoholic hepatitis at lower doses of alcohol consumption compared with men.[8] Moreover, women tend to present with more severe liver disease.[8]

Our patient presented approximately 7 years after her Roux-en-Y gastric bypass. In the 7 years preceding her admission, she had periods of heavy alcohol use. In fact, 1 year prior, she completed a 2-month inpatient rehabilitation program for her alcohol abuse.

4. **Which of the following laboratory values is *most helpful* in determining prognosis and utility of steroids in patients with alcoholic hepatitis?**
   a. PT
   b. Leukocytes
   c. Albumin
   d. Sodium
   e. Creatinine

The Maddrey discriminant function (MDF) can be used to predict prognosis and indicate utility of steroids in patients with severe alcoholic hepatitis. This test uses PT and bilirubin to determine a score using the following formula: MDF = (4.6 × [PT - control PT]) + (serum total bilirubin). A score greater than 32 favors the use of steroids as the 30-day mortality at this level is greater than 35%.[9,10] Leukocytosis is common in liver injury given the acute inflammatory state; however, very high white blood cell counts (>57,000/μL) have been found to be associated with a poor prognosis.[11] Given that liver injury results in decreased hepatic synthesis of albumin, serum albumin levels may be lower than normal in patients with alcoholic hepatitis. Furthermore, patients with alcoholism are frequently malnourished and this can also contribute to the low albumin. Sodium and creatinine can be helpful in predicting mortality in patients with alcoholic hepatitis using the Model for End-stage Liver Disease (MELD) score. The MELD score is calculated using the following formula which includes the creatinine, bilirubin, INR, and sodium: MELD (initial) = 0.957 × ln(creatinine) + 0.378 × ln(bilirubin) + 1.120 × ln(INR) + 0.643. The MELD-Na score is performed when the initial value greater than 11 includes sodium.[12] Our patient had an initial MDF score of 98.1 and MELD score of 30, both indicative of poor prognosis.

5. **Which of the following treatment regimens would be *most appropriate* for our patient?**
   a. Conservative management without steroids
   b. 7-day course of prednisolone 40 mg/d with another 21 days if signs of response
   c. Etanercept 25 mg twice weekly for 3 weeks
   d. Oxandrolone 10 mg two times daily for 1 month
   e. Urgent evaluation for liver transplant

Conservative management for alcoholic hepatitis involves alcohol abstinence, hydration, and nutrition. Prevention of relapse with cognitive behavioral therapy coupled with medical therapy leads to improved outcomes.[13,14] Aggressive fluid hydration is essential as poor oral intake before presentation is common in patients with alcoholic hepatitis. In patients who have concomitant pre-renal kidney injury, the use of albumin is recommended.[13] Many patients who present with alcoholic hepatitis are also malnourished and thus require additional nutritional support. These patients should be replenished with vitamins such as thiamine and folate. In patients who are severely malnourished, serum phosphate, potassium, and magnesium should be closely monitored given the risk of refeeding syndrome.[13] Although the treatment of severe alcoholic hepatitis remains a controversial topic, current recommendations call for supportive care with hemodynamic and nutritional support along with steroids in patients with an MDF greater than 32. The current guidelines recommend trialing prednisolone for a 7-day period and then re-evaluating the patient for response before proceeding with the final 21 days of treatment.[13] The Lille score which incorporates age, renal function, albumin, PT, bilirubin, and evolution of bilirubin at day 7, may be used to determine response to steroid treatment with a score >0.45 predicting nonresponse.[15] Before initiation of prednisolone, infection must be ruled out as alcoholic hepatitis often mimics sepsis with tachycardia, leukocytosis, fever, and hypotension. Etanercept is not effective for the treatment of alcoholic hepatitis and has been associated with higher 6-month mortality compared to placebo.[16] Treatment with anabolic steroids has failed to show beneficial effects related to mortality in patients with alcoholic liver disease.[17] Urgent evaluation for liver transplantation should be undertaken in patients with acute liver failure. Traditionally, consideration for liver transplant required a 6-month period of abstinence. However, it has been shown that early liver transplantation can improve survival in patients with a first episode of alcoholic hepatitis who do not initially respond to medical therapy.[18] Opinion on this issue is shifting and highly select patients with careful comprehensive risk assessment are increasingly being considered for urgent liver transplantation on a case-by-case basis. This remains controversial and additional studies are needed.

Our patient received an initial 7-day course of oral prednisolone. At the end of this period, repeat labs were notable for a significant decrease in serum bilirubin and INR. Given this positive response, steroids were continued for a full 28-day course with continued improvement in patient's abdominal pain and jaundice. Ultimately, she was referred to addiction psychiatry for further treatment of her alcohol use disorder.

DISCUSSION

Alcoholic hepatitis in an increasingly common condition in the United States that presents with acute hepatic injury in a patient who actively consumes or has history of consuming excessive amounts of alcohol.[19] (Alcoholic hepatitis is defined as rapid onset of jaundice with elevated serum AST arising in the background of heavy alcohol use.[20]) Notably, a liver biopsy is not required for diagnosis of alcoholic hepatitis. Alcoholic hepatitis is not a form of acute liver failure, but rather represents acute on chronic liver failure.

The National Institute on Alcohol Abuse and Alcoholism defines a standard drink as either 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.[21] Individuals are considered low-risk for developing alcohol use disorder when alcohol consumption is as follows: no more than 3 drinks on a single day and no more than 7 drinks per week for women and no more than 4 drinks on a single day and no more than 14 drinks per week for men.[22]

As alcohol consumption in the United States continues to increase, so too will the incidence of alcoholic hepatitis. Mild disease can be safely managed with conservative therapies including alcohol abstinence, hydration, and nutrition with positive outcomes. Severe disease portends a poor prognosis with 1-month

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mortality rates as high as 25% to 45%.[13] Therefore, severe disease requires treatment with steroids in addition to supportive therapy. Prednisolone reduces the 28-day mortality from alcoholic hepatitis but does not improve outcomes at 90 days or 1 year.[23] Therefore, benefits with prednisolone use are short-term. Pentoxifylline does not improve survival in patients with alcoholic hepatitis.[23] The most common causes of death in patients with alcoholic hepatitis are hepatic failure, gastrointestinal bleeding, and sepsis.[13]

The most important factor in predicting patient outcomes may be whether the patient is able to remain abstinent after the initial episode of alcoholic hepatitis. In patients who survived their initial hospitalization, the 5-year survival rate was 75% in those who remained abstinent compared to 27% in those who had a period of abstinence followed by relapse and 21% in those who continued drinking.[13] Therefore, referral to addiction psychiatry before discharge is of extreme importance for patients with alcohol use disorder to maximize chances of long-term remission.

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CORRECT ANSWERS: 1. b. 2. b. 3. c. 4. a. 5. b