A 73-year-old woman presented to the emergency department with a 3-month history of pruritus, jaundice, and recent mental status changes. Cirrhosis secondary to chronic hepatitis B virus infection had been diagnosed 3 months previously at an outside hospital. Hepatitis B virus treatment was not initiated at that time. There were no other notable comorbidities. Family members reported a 1-month increase of confusion, cognitive decline, anorexia, unintentional weight loss, and tremulousness. Furthermore, the patient reported increasing abdominal girth, lower extremity edema, and light-colored stools. She did not have fever or chills, night sweats, abdominal pain, hematemesis, or rectal bleeding.

Except for Asian descent, there were no risk factors for viral hepatitis. Her immunization history was unknown, and her family history was noncontributory. She had no history of tobacco, alcohol, or intravenous drug use. Medications included spironolactone, desloratadine, and cholecalciferol. There had been no recent changes of her medications.

Physical examination revealed cachexia and a body mass index of 19.8 kg/m². The patient was afebrile and oriented to time, place, and person. She had scleral icterus, jaundice, scattered skin ecchymoses, and bilateral eyelid xanthelasmas. Spider nevi were present on her upper torso, but other stigmata of chronic liver disease were absent. Cardiopulmonary examination results were unremarkable. The abdomen was nontender and mildly distended with flank dullness. The liver edge was firm and palpated 2 cm below the costal margin with a percussive length of 12 cm. No splenomegaly was noted. She had a rhythmic flapping tremor of the wrists consistent with asterixis. There were no focal neurologic findings.

Initial laboratory testing revealed the following (reference ranges provided parenthetically): hemoglobin, 9.2 g/dL (12.0-15.5 g/dL) with a mean corpuscular volume of 101 fl.; leukocytes, 6.4 × 10⁹/L (3.5-10.5 × 10⁹/L); platelet count, 126 × 10⁹/L (150-450 × 10⁹/L); activated partial thromboplastin time, 40 seconds (28-38 seconds); prothrombin time, 19.6 seconds (9.5-13.8 seconds); international normalized ratio, 1.7 (0.8-1.2); creatinine, 0.5 mg/dL (0.6-1.1 mg/dL); serum urea nitrogen, 14 mg/dL (6-21 mg/dL); sodium, 132 mmol/L (135-145 mmol/L); potassium, 3.9 mmol/L (3.6-5.2 mmol/L); albumin, 2.0 g/dL (3.5-5.0 g/dL); aspartate aminotransferase, 133 U/L (8-43 U/L); alanine aminotransferase, 97 U/L (9-50 U/L); alkaline phosphatase (AP), 145 U/L (10-100 U/L); total bilirubin, 15.5 mg/dL (0-1.2 mg/dL); and direct bilirubin, 11.9 mg/dL (0-0.3 mg/dL).

1. Which one of the following findings is most predictive of cirrhosis in a patient with liver disease?
   a. History of diabetes mellitus
   b. Ascites
   c. Spider nevi
   d. Platelet count of less than 160 × 10⁹/L
   e. Terry nails

   A meta-analysis assessed clinical indicators of cirrhosis in adults with known or suspected liver disease. Diabetes mellitus was the only historical feature that increased the likelihood of a patient having cirrhosis (likelihood ratio [LR], 2.8; 95% CI, 1.5-4.0). Ascites (LR, 7.2; 95% CI, 2.9-12) and spider nevi (LR, 4.3; 95% CI, 2.4-6.2) were reported to be the most reliable physical examination findings to predict the presence of cirrhosis because they had the narrowest CIs. Additionally, a platelet count of less than 160 × 10⁹/L was the laboratory finding most likely to predict cirrhosis, both when present or absent (positive LR, 6.3; 95% CI, 4.3-8.3; negative LR, 0.29; 95% CI, 0.20-0.39).
highest likelihood of predicting cirrhosis (LR, 16-22), even though no CI was calculated. Terry nails are characterized by a progressive ground glass–like opacity that extends from the base of the nail, making the lunula indistinguishable, to the distal border of the nail where it leaves a terminal band of normal “pink.” These nail changes are usually bilateral and symmetric with a tendency to be more marked in the thumb and forefinger. The pathophysiology of Terry nails is unknown. Terry nails are not exclusive to patients with cirrhosis and have been observed in congestive heart failure, type 2 diabetes mellitus, thyrotoxicosis, pulmonary eosinophilia, malnutrition, actinic keratosis, and advanced age.

Our patient did not have Terry nails on physical examination; however, several other important predictive findings of cirrhosis such as ascites, spider nevi, hepatomegaly (LR, 2.4; 95% CI, 1.2-3.6) and jaundice (LR, 3.8; 95% CI, 2.0-7.2) were present. In addition, laboratory studies revealed thrombocytopenia, hypoprotrombinemia (LR, 5.0; 95% CI, 3.2-6.9), and hypoalbuminemia (LR, 4.4; 95% CI, 1.5-7.3).

2. In view of the findings on clinical examination, which one of the following is the best next step in the management of this patient?
   a. Perform paper-and-pencil test
   b. Obtain serum ammonia level
   c. Initiate lactulose
   d. Initiate rifaximin
   e. Start polyethylene glycol (PEG)

The approach to a patient with hepatic encephalopathy (HE) should focus on 4 points: underlying disease, time course of presentation, severity of symptoms, and presence of precipitating factors. Regarding the underlying mechanism, HE can be attributed to acute liver failure (type A), portosystemic shunts (type B), or cirrhosis (type C). According to its time course, HE is subdivided into episodic, recurrent, or persistent. The West Haven criteria are the criteria standard for classifying the severity of HE. On the basis of the clinical presentation, the West Haven criteria divides HE into minimal, grade 1, grade 2, grade 3, and grade 4.

Additional testing to evaluate for etiologies of chronic liver disease was negative for hepatitis B surface antigen, hepatitis B core total antibody, and hepatitis C antibody and positive for hepatitis B surface antibody. Iron studies revealed a serum iron level of 175 μg/dL (35-145 μg/dL), total iron-binding capacity of 173
μg/dL (250-400 μg/dL), and a ferritin level of 376 μg/L (11-307 μg/L). The ceruloplasmin level was 35.8 mg/dL (16.0-45.0 mg/dL), and the α1-antitrypsin level was 185 mg/dL (100-190 mg/dL). Autoimmune serologies were negative for anti-smooth muscle antibodies and anti-liver-kidney microsome type 1 antibodies. The antimitochondrial antibody (AMA) titer was 1.4 U (<0.1 U).

Abdominal ultrasonography revealed scant ascites, cirrhotic liver contour, and no evidence of malignancy or extrahepatic biliary dilatation.

### 3. Which one of the following is the most likely cause of cirrhosis in this patient?

- a. Chronic hepatitis B virus infection
- b. Hemochromatosis
- c. Wilson disease
- d. Autoimmune hepatitis
- e. Primary biliary cholangitis (PBC)

The patient’s previous diagnosis of chronic hepatitis B virus infection was proved erroneous once serologic results indicated only prior vaccination for hepatitis B. In hemochromatosis, an elevated transferrin saturation (serum iron/total iron-binding capacity) is the earliest phenotypic abnormality, with serum ferritin levels greater than 200 mg/L in premenopausal and 300 mg/L in postmenopausal women suggestive of hemochromatosis. However, liver injury related to hemochromatosis is usually associated with ferritin levels higher than 1000 ng/mL. Marked elevations in serum ferritin and increased transferrin saturation are not specific to hemochromatosis and can be associated with chronic inflammation, malignancy, and cirrhosis. Even though both transferrin saturation (>90%) and ferritin level (376 μg/L) are elevated in our patient, the lack of specificity of these levels, in combination with the absence of other findings, make the diagnosis of hemochromatosis unlikely. Among metabolic causes, Wilson disease and α1-antitrypsin deficiency are unlikely because the patient’s ceruloplasmin and α1-antitrypsin levels, respectively, are normal. In addition, the patient’s older age argues against the diagnosis of Wilson disease. Autoimmune hepatitis is less likely given the negative serologic results for anti-smooth muscle and anti-liver-kidney microsome type 1 antibodies.

The diagnosis of PBC can be established when 2 of the following 3 criteria are met: (1) biochemical evidence of cholestasis based mainly on AP elevation; (2) presence of AMA; and (3) histologic evidence of nonsuppurative destructive cholangitis with destruction of interlobular bile ducts. Our patient had an elevated AP level of 452 U/L and total bilirubin level of 15.5 mg/dL. Additionally, her AMA titer was positive. She also had typical manifestations of PBC, including eyelid xanthelasmas, chronic fatigue, and pruritus. The presence of 2 of the diagnostic criteria, in addition to the characteristic clinical findings, confirmed PBC as the etiology of her cirrhosis. With an established diagnosis and resolution of overt HE, she was discharged from the hospital with scheduled outpatient follow-up.

### 4. In the outpatient setting, which one of the following is the best next step in the management of this patient’s liver disease?

- a. Liver ultrasonography
- b. Esophagogastroduodenoscopy (EGD)
- c. Nonselective β-blocker therapy
- d. Transjugular intrahepatic portosystemic shunt placement
- e. Liver biopsy

Patients with advanced liver disease should be intermittently monitored for disease progression and complications. The development of hepatocellular carcinoma (HCC) and variceal hemorrhage are 2 major complications of advanced liver disease. Cirrhotic patients should be screened every 6 months with liver ultrasonography to monitor for development of HCC. Even though ultrasonography is routinely used for HCC screening, magnetic resonance imaging and computed tomography of the liver have superior sensitivity in the detection of HCC, especially in patients in whom clinical suspicion for HCC is high. Our patient had undergone liver ultrasonography in the hospital, which revealed no HCC; therefore, repeated liver ultrasonography is not required at this time.

On diagnosis of cirrhosis, every patient should undergo EGD to assess for the presence and severity of gastroesophageal varices, which will determine whether prophylaxis for variceal bleeding should be initiated. Patients with portal
hypertension and no endoscopic evidence of varices should be monitored with screening EGD every 2 to 3 years. Administering β-blockers for prevention of gastrointestinal tract bleeding in patients without varices is not beneficial and has been associated with increased complications. Nonselective β-blockers should be used to prevent bleeding in patients with small varices and increased risk for hemorrhage or in those with medium or large varices that have not yet bled. Patients who have survived an episode of variceal hemorrhage, regardless of the size of the varices, benefit from β-blockade initiation. Once β-blockers are started, surveillance EGD is not necessary.9

The use of transjugular intrahepatic portosystemic shunts or surgical shunts is currently limited to patients with active bleeding or no response to medical and endoscopic treatment or for the management of refractory ascites. Liver biopsy is required in only 10% of cases of PBC that present with negative AMA findings and in a minority of AMA-positive patients with AP levels less than 1.5 times the upper limit of normal (ULN) or aspartate aminotransferase levels more than 5 times the upper limit of normal. Liver biopsy may also be necessary to exclude other concomitant diseases such as autoimmune hepatitis or nonalcoholic steatohepatitis.10 Our patient already met the diagnostic criteria for PBC and does not require liver biopsy confirmation.

Our patient underwent EGD, which revealed no evidence of gastroesophageal varices.

5. Which one of the following is the best treatment for this patient’s condition?
   a. Ursodeoxycholic acid (UDCA)
   b. Cholestyramine
   c. Mycophenolate
   d. Prednisone
   e. Azathioprine

Before deciding on pharmacological management of PBC, it is important to consider prognosis. The Model for End-Stage Liver Disease (MELD) score estimates patient mortality on the basis of serum creatinine concentration, serum bilirubin level, and prothrombin time. Individuals with a MELD score greater than 15 should be referred for liver transplant.11 Our patient’s MELD score on admission was 23, predicting a high (19.6%) 3-month mortality.

Ursodeoxycholic acid is the only therapy for PBC approved by the US Food and Drug Administration. The use of UDCA improves survival and may reduce the need for liver transplant. It can be used in any stage of PBC; however, earlier histologic stages of PBC tend to respond more favorably to UDCA. The effect of treatment can be monitored by a decrease of serum AP. Ursodeoxycholic acid has not been found to improve fatigue, bone disease, or pruritus. Bile acid sequestrants (eg, cholestyramine) should be used as initial therapy for patients with PBC who have pruritus. Pruritus refractory to cholestyramine can be treated with rifampin, naltrexone, or sertraline. Corticosteroids and other immunosuppressants (eg, mycophenolate and azathioprine) have been tested and found to have no beneficial role in the treatment of PBC.7

Our patient presented with advanced PBC. Even though there were no contraindications to initiating UDCA, the benefits of this therapy are limited in advanced PBC. She was not considered a candidate for liver transplant because of her clinical state and comorbidities. After discussion of prognosis with the patient and her family, she opted for supportive care to improve quality of life and decrease symptoms.

DISCUSSION
On the basis of our patient’s clinical presentation, physical examination features, and laboratory findings, we diagnosed cirrhosis complicated by HE. This case highlights the diagnostic importance of physical examination findings and basic laboratory testing in patients with suspected cirrhosis. Approximately 15% of cirrhotic patients exhibit signs of overt HE on initial presentation. Early identification and a stepwise approach to encephalopathic patients are critical in order to decrease mortality. Furthermore, screening for HCC and prevention of variceal bleeding remain the biggest challenges in decreasing mortality in patients with advanced liver disease.

Determining the cause of cirrhosis is important for disease management and prognosis. Among autoimmune etiologies, PBC is characterized by nonsuppurative inflammation and destruction of the interlobular bile ducts with variable progression to cirrhosis. The prevalence of PBC is 40 per 100,000 persons, with 90% of
affected individuals being women. The cause of PBC is likely autoimmune with genetic and environmental factors involved. Potential environmental triggers include smoking, urinary tract infections, and various microorganisms. Genetic susceptibility alleles for PBC have been identified. There are ongoing clinical trials to identify new drugs and alternative treatments for PBC that is unresponsive to UDCA. Most notably, obeticholic acid and bezafibrate have been promising for nonresponders to UDCA in phase 2 clinical trials. Although therapeutic progress has been seen in the past 5 to 10 years, a substantial number of patients still require liver transplant. Until new therapies are available that improve quality of life and increase survival of patients with PBC, early diagnosis, treatment, and surveillance for complications will remain essential to improve PBC disease outcomes.

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REFERENCES

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