73-Year-Old Man With Increasing Abdominal Girth and Dyspnea

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A 73-year-old man with a history of type 2 diabetes mellitus, hyperlipidemia, and obesity presented to the emergency department with a 3-month history of increasing abdominal girth and shortness of breath. He also noted some mild abdominal discomfort when he moved. He denied nausea, vomiting, diarrhea, constipation, chest pain, fevers, and significant alcohol use. His medications included amlodipine, aspirin, glyburide, and hydrochlorothiazide.

On examination, the patient was afebrile, and he had a heart rate of 65 beats/min, a blood pressure of 150/70 mm Hg, and a respiratory rate of 20 breaths/min. His cardiac examination had no extra heart sounds, and his jugular venous pressure (JVP) was not elevated. His lungs were clear. The patient's abdomen was tightly distended and painful with deep palpation without rebound or guarding; shifting dullness was present. He had no stigmata of chronic liver disease. Findings on lymphatic, skin, thyroid, and musculoskeletal examinations were unremarkable. Electrocardiography revealed nonspecific T-wave abnormality and a prolonged corrected QT interval of 459 ms. Chest radiographic findings were normal. Laboratory studies yielded the following results (referential ranges provided parenthetically): hemoglobin, 14.2 × 109/L (13.5-17.5 g/dL); leukocytes, 5.2 × 109/L (4.0-10.0 × 109/L); platelets, 63 × 109/L (150-450 × 109/L); creatinine, 1.4 mg/dL (0.8-1.3 mg/dL); glucose, 199 mg/dL (70-140 mg/dL); aspartate aminotransferase, 38 U/L (8-48 U/L); alanine aminotransferase, 24 U/L (7-55 U/L); total bilirubin, 0.4 mg/dL (0.1-1.0 mg/dL); and alkaline phosphatase, 120 U/L (45-115 U/L).

1. Which one of the following would be the first diagnostic test to obtain in this patient?
   a. Serum alpha-fetoprotein
   b. Ultrasonography of the liver
   c. Brain natriuretic peptide
   d. Abdominal paracentesis
   e. Hepatobiliary iminodiacetic acid (HIDA) scan (cholescintigraphy)

This patient has new-onset ascites and abdominal discomfort. Life-threatening conditions, such as spontaneous bacterial peritonitis (SBP), need to be ruled out before investigating the etiology of the ascites. Although serum alpha-fetoprotein has been associated with liver disease and malignancy, it would not be an urgent test to obtain. Ultrasonography of the liver would be useful to determine structural abnormalities of the liver and biliary tree; however, it would not aid in ruling out SBP. Brain natriuretic peptide levels are elevated in those with heart failure; however, this patient lacks signs of heart failure (eg, elevated JVP, S3 gallop, and pulmonary crackles). Brain natriuretic peptide may be useful to determine the etiology of his ascites once urgent conditions are managed.

In patients with new-onset ascites, paracentesis is necessary to rule out infection and aid in etiology determination. Spontaneous bacterial peritonitis is present in 1.5% to 3.0% of outpatients with cirrhosis and ascites and up to 10% of inpatients. The mortality rate from SBP has decreased from approximately 90% to 20% because of early diagnosis and treatment; therefore, early analysis of ascitic fluid is important to help decrease mortality. An HIDA scan can detect abnormalities of the gallbladder and biliary tree. The patient's clinical presentation is not suggestive of conditions that would lead to abnormalities on HIDA scan (eg, acute cholecystitis, bile leak).

The patient underwent paracentesis, and 2.2 L of clear yellow fluid was removed. Analysis of the ascitic fluid revealed the following: total protein, 1.3 g/dL; albumin, 58.0%; total nucleated cells, 485/mcL; and neutrophils, 60.0%. Mesothelial cells were also present. The patient's serum albumin was 3.1 g/dL (3.5-5.0 g/dL), and his serum total protein was 6.7 g/dL (6.3-7.9 g/dL).

2. Which one of the following is the most likely etiology of ascites in this patient?
   a. Pancreatitis
   b. Mesothelioma
   c. Cirrhosis
   d. Peritoneal carcinomatosis
   e. Heart failure

The serum ascites albumin gradient (SAAG) is the preferred method for determining the cause of ascites. The patient's SAAG was 2.3 g/dL, calculated by subtracting the ascitic fluid albumin concentration (0.8 g/dL) from the serum albumin concentration (3.1 g/dL). A value
greater than 1.1 g/dL indicates elevated portal pressures and is associated with conditions such as cirrhosis and heart failure. Notably, heart failure is associated with a high SAAG and a high total ascitic fluid protein, distinguishing it from portal hypertension due to cirrhosis. A SAAG less than 1.1 g/dL is associated with diseases that increase ascitic fluid protein, such as malignancies, tuberculosis, pancreatitis, and nephrotic syndrome. Pancreatitis and mesothelioma are unlikely etiologies of this patient's ascites given his high SAAG. Cirrhosis is a likely etiology because his SAAG is greater than 1.1 g/dL and cirrhosis is relatively common. Peritoneal carcinomatosis would increase ascitic fluid protein and would be associated with a low SAAG. Heart failure is associated with a high SAAG; however, the patient's normal JVP and unremarkable findings on cardiac and pulmonary examinations make this less likely.

Ultrasonography of the right upper quadrant was performed. The liver had a coarse echotexture consistent with chronic parenchymal disease. The spleen, gallbladder, and biliary tree appeared normal. Doppler studies showed normal flow. Transthoracic echocardiography showed a normal ejection fraction and no valvular abnormalities.

3. Which one of the following is the most likely cause of cirrhosis in this patient?
   a. Nonalcoholic fatty liver disease (NAFLD)
   b. Medications
   c. Wilson disease
   d. α₁-Antitrypsin deficiency
   e. Budd-Chiari syndrome

   Given this patient’s history of diabetes, obesity, and hyperlipidemia, NAFLD is the likely cause of his cirrhosis. Its prevalence is 20% to 40% in Western countries and progresses to cirrhosis in up to 20% of cases. A concurrent diagnosis of type 2 diabetes and obesity are correlated with the progression of NAFLD to fibrosis. The patient was not taking a medication known to cause cirrhosis. Medications commonly associated with chronic liver disease include disease-modifying anti-rheumatic drugs and highly active anti-retroviral therapy. Wilson disease is a disorder of copper metabolism that typically presents before the age of 40 years, making it unlikely in this patient. Patients with Wilson disease can develop neuropsychiatric symptoms, anemia, renal disease, and cirrhosis. α₁-Antitrypsin deficiency is a storage disease that causes emphysema and cirrhosis. This patient had no lung involvement, making this diagnosis unlikely. Budd-Chiari syndrome is occlusion of the hepatic veins leading to portal hypertension. If this syndrome had been present in this patient, it would likely have been detected on ultrasound Doppler studies of the liver.

A liver biopsy showed portal tracts expanded by fibrosis with portal-to-portal bridging and nodule formation. The interlobular bile ducts, portal vein branches, and hepatic arterioles appeared unremarkable. There was macrovesicular steatosis in the hepatic acinar parenchyma. Neither cholestasis nor significant necro-inflammatory activity was observed, and the iron stain was negative.

4. Which one of the following treatments should be recommended to treat this patient’s NAFLD?
   a. Weight loss
   b. Vitamin D
   c. Ursodeoxycholic acid
   d. Vitamin E
   e. N-acetylcysteine

   Many treatments have been studied in patients with NAFLD, but few have shown benefit. Because no definitive treatment is available for NAFLD, the current goals of treatment are to control the underlying risk factors, such as obesity and diabetes. Therefore, weight loss through dietary and lifestyle modifications is indicated in all patients with cirrhosis secondary to NAFLD. Vitamin D supplementation has no role in the treatment of NAFLD. Ursodeoxycholic acid has been investigated in the treatment of NAFLD because of its role in decreasing apoptosis; thus far, studies have been inconclusive, and it is therefore not recommended. Vitamin E supplementation has shown inconsistent results with regard to improving fibrosis, and therefore providing patients with supplemental vitamin E is not currently recommended. N-acetylcysteine is a treatment for acute acetaminophen toxicity and is not indicated for treatment of NAFLD.

   The patient underwent upper endoscopy, and small varices were noted. He was discharged from the hospital with recommendations for fluid and sodium restriction, propranolol, furosemide, and spironolactone. He was given an appointment to follow up as an outpatient.

5. If this patient requires SBP prophylaxis in the future, which one of the following antibiotics should be recommended?
   a. Norfloxacin
   b. Clindamycin
   c. Cefotaxime
   d. Amoxicillin
   e. Sulfamethoxazole-trimethoprim

   Indications for SBP prophylaxis include a history of SBP, low ascitic fluid protein concentrations, and gastrointestinal bleeding. Norfloxacin has been the most wide-
ly used antibiotic for prophylaxis. However, this patient has a prolonged QT interval, making norfloxacin a poor choice. Clindamycin does not have the correct coverage spectrum to be used as a prophylactic antibiotic for SBP. Cefotaxime is an intravenous antibiotic that is used to treat SBP but is not used for prophylaxis. Amoxicillin is not used for SBP prophylaxis. Sulfamethoxazole-trimethoprim is an alternative to norfloxacin for SBP prophylaxis and would be the best choice for this patient.

The patient returned to the gastroenterology clinic 2 weeks later for follow-up. He was adherent to the recommended fluid and sodium restrictions. He had also initiated moderate aerobic exercise by walking. On examination, his ascites had reaccumulated but not to the point of needing a second paracentesis. His medications were not changed, and he was scheduled to return in 1 month.

**DISCUSSION**

Nonalcoholic fatty liver disease encompasses a spectrum of diseases involving fatty deposition in the liver. The disease begins with steatosis, becomes nonalcoholic steatohepatitis when inflammation is present, and can end with cirrhosis. It is a leading cause of cryptogenic cirrhosis. The histologic changes in NAFLD are similar to those in alcoholic liver disease; however, they occur in patients who report drinking little alcohol (<20 g daily [<.7 oz]). The prevalence of NAFLD ranges from 20% to 40% in Western countries and progresses to cirrhosis in up to 20% of cases. Diabetes, obesity, and ethnicity influence the risk of developing NAFLD. The prevalence of NAFLD ranges from 2.7% in lean persons to greater than 50% in obese diabetic patients. Those of Hispanic origin are at the highest risk of developing NAFLD, and those of African origin are at the lowest risk.

The diagnosis of NAFLD should be suspected in patients with metabolic syndrome and abnormal liver enzymes. Because of the high prevalence of NAFLD, the diagnosis needs to be considered in any patient with elevated liver enzyme levels. Although imaging studies, such as ultrasonography, computed tomography, and magnetic resonance imaging, can be useful in evaluating elevated liver enzyme levels, the diagnosis of NAFLD can be confirmed only by liver biopsy. Magnetic resonance elastography is currently being used to determine the degree of liver fibrosis; however, biopsy remains the method to confirm diagnosis. Information gleaned from liver biopsy can also help determine the severity and prognosis of disease.

To prevent progression, management of NAFLD should focus on risk factor modification, such as the targeting of obesity, insulin resistance, and dyslipidemia. Moreover, gemfibrozil, metformin, vitamin E, thiazolidinediones, and statins have all been investigated in the treatment of NAFLD, but results have been mixed. In more advanced NAFLD, complications (eg, ascites, SBP) should be carefully managed. The mainstays of ascites management include sodium restriction, diuretics, aldosterone antagonists, and large-volume paracentesis. Prophylaxis for SBP can be given to those with a history of SBP, low ascitic fluid protein concentrations, and gastrointestinal bleeding.

The prognosis of patients with NAFLD varies depending on the severity of the disease. Why NAFLD progresses to nonalcoholic steatohepatitis and then cirrhosis is not well understood. In about half of patients with NAFLD, the disease does not progress. The disease can regress in the smaller fraction (about 25%) of patients who can implement aggressive lifestyle modifications. Of patients who develop cirrhosis, 20% to 40% will die of a liver-related cause in a 10-year period. Therefore, it is imperative that physicians counsel patients at risk to prevent this condition by early and aggressive management of risk factors such as obesity and diabetes.

**REFERENCES**


Correct answers: 1. d, 2. c, 3. a, 4. a, 5. e