New Onset Ascites Secondary to Cirrhosis

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CME INFORMATION

TARGET AUDIENCE

The January/February Clinical Case of the Month is intended for primary care physicians, general internists, surgeons, emergency room physicians, and gastroenterologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these manuscripts. After reading the article, the healthcare provider should be able to discuss the epidemiology, clinical manifestations, diagnosis, and treatment of ascites due to cirrhosis. Estimated time to complete this activity is one (1) hour.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

Drs. Richert and Raines have nothing to disclose.

Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees. He is also on the *Journal* Editorial Board.

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A 59-year-old man with a history of heavy alcohol use presented to the emergency department for evaluation of abdominal swelling and abdominal discomfort. He also reported scleral icterus, which had developed over the prior two days, and denied recent fever, chills, hematemesis, melena, chest pain, shortness of breath, or change in bowel habits. He drank six twelve-ounce beers daily for the past 30 years and denied any history of intravenous drug abuse, acetaminophen use, homemade tattoos, or blood transfusions. He was taking no prescribed medications.

Vital signs upon presentation included a temperature of 99.7° Fahrenheit, pulse of 145 beats per minute, blood pressure of 123/89 mmHg, and a respiratory rate of 13 breaths per minute. Pertinent physical findings included drowsiness, scleral icterus, and tachycardia. His abdominal exam revealed a distended, nontender abdomen with normoactive bowel sounds. The liver measured 12 cm in the right midclavicular line, and no spleen tip was palpated. Pitting edema was present in his lower extremities. His neurological exam demonstrated asterixis, and skin examination revealed spider angiomas over his chest wall but no evidence of palmar erythema or tattoos.

His admission laboratory values revealed a serum sodium of 134 mmol/L (135-146 mmol/L), potassium of 3.0 mmol/L (3.6-5.2mmol/L), chloride of 94 mmol/L (96-110mmol/L), creatinine of 0.8 mg/dL (0.8-1.5 mg/dL), blood urea nitrogen of <5 mg/dL (7-25 mg/dL), glucose of 126 mg/dL(65-99 mg/dL), total protein of 6.8 gm/dL (6-8 gm/dL), albumin of 2.4 gm/dL (3.4-5.4 gm/dL), total bilirubin of 7.0 mg/dL (<1.3 mg/dL), AST of 102 U/L (<45 U/L), ALT 40 U/L (<46 U/L), alkaline phosphatase of 235 U/L (20-120 U/L), acetaminophen level <10 µg/mL (10-20 µg/mL), a nonreactive acute hepatitis panel, and an ammonia level of 71 µmol/L (9-35 µmol/L). His white blood cell count was $6.8x10^3$/µL ($4.5-11x10^3$/µL); platelet count of $107x10^3$/µL ($130-400x10^3$/µL), and a hemoglobin and hematocrit of 13.4 gm/dL (13.5-17.5 gm/dL) and 38.7 percent (40-51 percent), respectively, were reported. Coagulation studies demonstrated a prothrombin time of 14.2 sec (9.5-12.5 sec), INR of 1.3 (0.9-1.1), and a normal

partial thromboplastin time of 31.6 sec. A paracentesis revealed a white-cell count of 7/µL with 26% segmented neutrophils, an albumin of less than 1.0 g/dL, and total protein less than 3.0 g/dL. An abdominal ultrasound was significant for the presence of ascites and a cirrhotic appearing liver.

The patient was admitted to the hospital for further evaluation and treatment of alcohol withdrawal and decompensated cirrhosis. He was treated with benzodiazepines, lactulose and a low sodium diet. He was also placed on a diuretic regimen of furosemide 40 mg orally daily along with spironolactone 100 mg orally daily. Once the patient was stable he was discharged home with close follow-up. He was seen in clinic one week after discharge at which time the patient stated he had not had any alcohol intake, and his abdominal girth had decreased.

INTRODUCTION

The three major complications of cirrrhosis include ascites, hepatic encephalopathy, and variceal hemorrhage.[1] Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. In this patient population, variceal hemorrhage occurs at a yearly rate of 5%-15% with a higher risk occurring in the patients with larger varices. Gastric varices are less prevalent than esophageal varices and occur in only 5%-33% of patients with portal hypertension. The reported incidence of bleeding in patients with gastric varices is about 25% over two years.[2] Another complication of cirrhosis is hepatic encephalopathy. Hepatic encephalopathy is a reversible decrease in neurologic function caused by liver disease. The onset is often insidious with subtle changes in memory, concentration, and reaction time, but progression of disease can lead to somnolence and sometimes coma.[3] The third major complication of cirrhosis is ascites. Our patient represents a case of ascites secondary to alcoholic cirrhosis, and this article will focus on the epidemiology, pathophysiology, clinical presentation, diagnostic work-up, and treatment of this disease process.

HISTORY/EPIDEMIOLOGY

Ascites, which is derived from the Greek word *askos*, ie, a leather bag used to carry wine, water or oil, was first recognized by Hippocrates to be a consequence of a diseased liver. Hippocrates also recognized that it was associated with a grim prognosis.[4] Today ascites is the most common of the three major complications of cirrhosis.[1] Of note, cirrhosis was the 12th leading cause of death in the United States in 2000 and was responsible for more than 25,000 deaths in that same year.[5] In the United States, approximately 85% of patients with ascites have cirrhosis with the most common causes of cirrhosis including alcohol, chronic hepatitis C, and nonalcoholic steatohepatitis related to obesity.[6] Approximately 50% of patients with cirrhosis, who have not yet suffered one of the three major complications of cirrhosis, develop ascites during ten years of observation. Roughly 50% of patients with cirrhosis who develop ascites will expire within two years.[1]

PATHOPHYSIOLOGY

In cirrhosis, the development of ascites occurs secondary to the combined effects of portal hypertension and plasma volume expansion. As the fibrosis of the liver worsens and regenerative nodules develop, sinusoidal hypertension occurs as hepatic venous outflow is obstructed.[4] Sinusoidal hypertension will eventually lead to portal hypertension. As portal hypertension develops, local production of vasodilators increases as well, most notably nitric oxide. This increase in vasodilators leads to splanchnic arterial vasodilation.[7] In the early stages of cirrhosis, the splanchnic arterial vasodilation is moderate and has a very small effect on the effective arterial blood volume (EABV). At this stage, the small decrease in the EABV can be compensated by an increase in plasma volume and cardiac output.[8] The increase in plasma volume is secondary to sodium retention, which is increased with the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Plasma volume is also increased by an increase in antidiuretic hormone, which leads to free water retention and hyponatremia.[4] In the late stages of cirrhosis, the decrease in EABV is so severe that it leads to a decrease in arterial pressure which leads to sodium and fluid retention. The combination of splanchnic arterial vasodilation and portal hypertension then leads to changes in the intestinal capillary pressure and permeability, making accumulation of retained fluid in the abdomen more likely.[5]

CLINICAL PRESENTATION

The most common manifestations associated with new onset ascites are recent weight gain and an increase in abdominal girth. The abdominal girth is usually described as tightness of garments around the waist or belt.[4] Ascites can usually be suspected by the protuberance of the abdomen along with the patient's history, but there are other conditions that can mimic this clinical picture and should be kept in mind while evaluating a patient with presumed ascites, including obesity, gas, ovarian masses, and pregnancy.

When ascites is suspected by history, a physical exam, along with an imaging test, should be performed to help establish the diagnosis. Although a physical exam is used to help with determining the diagnosis, the accuracy of physical findings is often affected by a number of factors. These include the amount of fluid present, the technique used to examine the patient, and the clinical setting, ie, it may be more difficult to detect ascites in an obese patient versus a thin patient. One study reported that the sensitivity and specificity of the physical exam to detect

ascites ranged between 50%-94% and 29%-84% respectively when compared to ultrasound as the gold standard.[9] On the other hand, the absence of flank dullness is 90% accurate in predicting the absence of ascites. However, 1500 mL of fluid needs to be present in order for flank dullness to be detected; thus, lesser amounts of ascites can be missed. In situations such as this, ultrasonography is recommended to help establish the diagnosis.[10] The abdominal ultrasound can also be used to rule out the presence of hepatic vein obstruction, which is an often-overlooked cause of ascites. The diagnosis of new onset ascites is usually suspected on the basis of a patient's history and physical exam and confirmed by paracentesis or abdominal imaging. The cause of the ascites, on the other hand, is based on the history, physical exam, and analysis of the ascitic fluid.[1]

DIAGNOSTIC WORK-UP

Abdominal paracentesis with ascitic fluid analysis is the most cost-effective method of diagnosing the cause of ascites. Ascitic fluid should be sampled in all inpatients and outpatients with new onset ascites.[6] If uncomplicated cirrhotic ascites is suspected, the initial specimen of ascitic fluid should be sent for cell count and differential, albumin, and total protein concentration. With the results of the aforementioned tests, the serum-ascites albumin gradient (SAAG) can be calculated. This involves measuring the serum albumin and the ascites albumin on the same day and subtracting the ascitic fluid value from the serum value. A value greater than or equal to 1.1 g/dL is diagnostic for portal hypertension with an accuracy of approximately 97%.[11] In the event a patient with new onset ascites presents with suspected ascitic fluid infection, ie, fever, abdominal pain, or unexplained encephalopathy, the ascitic fluid specimen should also be sent for culture in blood culture bottles.[1] Ascites cultures can be negative in up to 40% of patients with clinical manifestations of spontaneous bacterial peritonitis (SBP) and an elevated polymorphonuclear cell count in the ascitic fluid.[12] Therefore, the presumed diagnosis is made when the polymorphonuclear count of the ascitic fluid is >250/mm^3 and/or a positive ascitic fluid culture[13] is present without evidence of an intrabdominal process requiring surgical treatment.[6]

TREATMENT

The appropriate initial treatment of ascites due to cirrhosis of the liver involves addressing the underlying disease, sodium restriction, and diuretics.[1] In the case of a patient with underlying alcoholic liver disease, abstinence can result in healing of the reversible component of alcoholic liver disease within a matter of months, enabling the ascites

to resolve or become more responsive to medical treatment. Other liver diseases causing cirrhosis are less reversible, and by the time of onset of ascites the patient may be a transplant candidate rather than a candidate for long-term medical treatment. It is also recommended that patients take in no more than 1500 mg to 2000 mg of sodium per day.[1] This restriction of sodium may help eliminate ascites as well as prevent its reaccumulation. A more stringent restriction is usually poorly tolerated by the patient and therefore is not recommended. The last step in the initial treatment of ascites is the initiation of diuretics. The usual diuretic regimen consists of once daily dosing of oral spironolactone and furosemide, beginning with 100 mg and 40 mg doses, respectively. If the goals of appropriate weight loss and natriuresis (urinary excretion of sodium >78 mmol per day) are not met, the doses can be doubled every three to five days until the maximum daily doses of spironolactone (400 mg) and furosemide (160 mg) are reached. Patients with massive edema have no maximum daily weight loss goal, but a patient with no peripheral edema should have a maximum weight loss goal of no more than 0.5 kg/day.

In the situation where the above measures are not successful in mobilizing ascitic fluid, a patient may be considered to have refractory ascites. Refractory ascites can be either diuretic resistant ascites or diuretic intractable ascites. Diuretic resistant ascites is defined as failure to lose at least 1.5 kilogram per week of fluid weight despite maximal diuretic therapy as described above, or equivalent doses of a distal-acting and a loop acting diuretic, respectively. Diuretic intractable ascites is defined as ascites that is difficult to mobilize because of the inability to provide effective doses of diuretics secondary to diuretic-induced adverse effects, such as azotemia or hyponatremia. Treatment options for refractory ascites include repeated large-volume paracentesis (LVP) and transjugular intrahepatic portosystemic shunt (TIPS). A LVP, ie, when greater than five liters of ascitic fluid are removed during a single paracentesis, is sometimes associated with postparacentesis circulatory dysfunction. The risk of postparacentesis circulatory dysfunction can be reduced by administering albumin intravenously in a dose of 6-8 grams per liter of ascites removed.[14] A TIPS, which can be placed by an interventional radiologist, is a shunt that connects the portal and hepatic veins, leading to a decrease in the transhepatic pressure gradient. When compared head to head, TIPS is found to be superior to repeated LVP for long-term control of ascites but without any effect on transplant-free survival.[15] Additionally, for the same survival outcomes, TIPS is less cost-effective than LVP for the control of refractory ascites. Therefore, TIPS is best reserved for patients who have failed repeated LVP and have preserved liver function, defined as creatinine < 1.5 mg/dL, an international normalized ratio <1.5, and a bilirubin level < 2 mg/dL. Ideally TIPS should be used as a bridge to liver transplantation.[14]

A patient who has ascites secondary to cirrhosis should be referred for liver transplant evaluation since the presence of ascites is associated with poor long-term survival. Survival rates for patients who develop ascites are 30%-40% at five years compared to 70%-80% among patients who have had a liver transplant.[5] Evaluation for transplant should be considered for irreversible hepatic failure, complications of decompensated cirrhosis, systemic complications of liver disease, liver cancers, or liver-based metabolic conditions causing systemic disease.[16] The model of end-stage liver disease (MELD) score is a mathematical score that uses the patient's laboratory tests, creatinine, bilirubin, and international normalized ratio and is very predictive of a patient's short term mortality. In the United States, patients can be listed for transplantation at any MELD score but priority is assigned to patients with higher MELD scores.[5]

SBP is one of the common bacterial infections seen in patients with end stage liver disease (ESLD). The prevalence of SBP in ESLD patients admitted to the hospital with ascites has been estimated to range between 7%-23%. The one-year probability of an ESLD patient with ascites developing SBP is approximately 10%. In roughly 50% of the cases, the causative organism is found in culture of the ascitic fluid or blood specimen, with the most common causative organisms being *Escherichia coli*, *Klebsiella*, and other Enterobacteriaceae. There has also been a recent increase in methicillin-resistant *Staphylococcus aureus* causing SBP. The survival rate after development of SBP is poor, and patients should be considered for liver transplantation after an episode of SBP. It is recommended empirically to use a third generation cephalosporin, such as cefotaxime 2 grams intravenously every 12 hours for a minimum of five days, to treat SBP. Albumin has been shown to decrease the incidence of renal impairment and to improve hospital survival when compared to antibiotics alone. It should be given intravenously, along with antibiotics, at a dose of 1.5 grams per kilogram of body weight at the time of diagnosis, followed by 1 gram per kilogram of body weight on day three.[17]

In the past, patients admitted to the hospital with ascites as their major problem frequently occupied beds for a long period of time secondary to confusion regarding diagnosis and treatment. Today, it is not a prerequisite for a patient to have no evidence of ascites prior to discharge.[1] A patient can be discharged home if it can be documented that they are medically stable, are responding to medical and dietary treatment, and are normokalemic and not azotemic. The patient ideally should be seen in the outpatient clinic within one week of discharge.[6]

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CME QUESTIONS

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Choose the answer that is most correct for each question.

1. True/False
   Gastroesophageal varices are present in approximately 50% of patients with cirrhosis.

2. Spontaneous bacterial peritonitis, in the absence of an intraabdominal process requiring surgical treatment, is diagnosed when the polymorphonuclear cell count of the ascitic fluid is:
   a. >500/mm^3.
   b. >250/mm^3.
   c. >150/mm^3.
   d. >75/mm^3.

3. The Model of End-Stage Liver Disease is a score used to direct donor organs to those in greatest need. Which of the following patient laboratory values is used in this equation?
   a. Serum creatinine concentration.
   b. Total bilirubin.
   c. International normalized ratio.
   d. All of the above.

4. Which of the following statements is false?
   a. The risk of postparacentesis circulatory dysfunction can be reduced by administering albumin intravenously in a dose of 6-8 grams per liter of ascites removed during a large volume paracentesis.
   b. The one year probability of an ESLD patient with ascites developing SBP is approximately 10%.
   c. TIPS was found to be less cost-effective than LVP for the control of refractory ascites.
   d. It is recommended that patients with cirrhosis and ascites take in no more than 500mg of sodium per day.