MAYO CLINIC

# 57-Year-Old Woman With Abdominal Pain

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**See end of article for correct answers to questions.**

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A 57-year-old woman with no remarkable medical history presented to the emergency department with worsening right upper quadrant abdominal pain and nausea of 1 day's duration. Her vital signs included the following: temperature, 36.6°C; heart rate, 93 beats/min; respiratory rate, 14 breaths/min; and blood pressure, 164/86 mm Hg. She was alert and oriented. Physical examination findings were notable for absent breath sounds at bilateral lung bases, abdominal distention with shifting dullness, moderate tenderness on palpation of the right upper abdominal quadrant with a tender, smooth liver edge palpable 4 cm below the costal margin, 2+ pitting edema up to the knees bilaterally, and no asterixis. There were no signs of chronic liver disease.

Laboratory evaluation revealed the following (reference ranges provided parenthetically): hemoglobin, 18.9 g/dL (12.0-15.5 g/dL); mean corpuscular volume, 86.5 fL (81.6-98.3 fL); leukocyte count, 19.9 × $10^9$/L (3.5-10.5 × $10^9$/L); sodium, 134 mmol/L (135-145 mmol/L); potassium, 4.4 mmol/L (3.6-5.2 mmol/L); chloride, 100 mmol/L (98-107 mmol/L); creatinine, 1.5 mg/dL (0.6-1.1 mg/dL); aspartate aminotransferase (AST), 2538 U/L (8-43 U/L); alanine aminotransferase (ALT), 2563 U/L (7-45 U/L); alkaline phosphatase, 702 U/L (55-142 U/L); total bilirubin, 2.0 mg/dL (≤1.2 mg/dL); direct bilirubin, 0.9 mg/dL (0.0-0.3 mg/dL); and international normalized ratio, 1.7.

**1. Based on the clinical scenario, which *one* of the following diseases is *most likely* in this patient?**

a. Choledocholithiasis
b. Hepatic cirrhosis
c. Alcoholic hepatitis
d. Chronic hepatitis B infection
e. Acute hepatic vein thrombosis

Utilizing a systematic approach is crucial when interpreting abnormal liver enzyme levels. The pattern, rate, degree, and nature of alteration can aid in identifying the underlying etiology. Classically, elevation of AST and ALT indicates hepatocellular injury, while elevation of alkaline phosphatase and bilirubin indicates a cholestatic process. Accordingly, the marked elevation of AST and ALT in this case (>1000 U/L) suggests hepatocellular injury and narrows the differential diagnosis substantially.

Choledocholithiasis, or impaction of a gallstone within the common bile duct, can cause enzyme elevations greater than 1000 U/L but will not lead to the development ascites. Hepatic cirrhosis is the end result of long-standing chronic liver disease of various etiologies and is characterized by fibrosis and loss of functional hepatocytes. Without functional liver parenchyma, such a major increase in enzymes is not observed. Alcoholic hepatitis occurs in the setting of recent heavy alcohol use and will also cause hepatocellular injury. However, it does not present with liver enzyme elevation greater than 1000 U/L and is typically characterized by an AST to ALT ratio of 2:1. Chronic viral hepatitis B is a smoldering inflammatory process that will cause hepatocellular injury and liver enzyme elevation but not greater than 1000 U/L. Acute hepatic vein thrombosis, also known as Budd-Chiari syndrome, can cause an extreme elevation in liver enzymes of greater than 1000 U/L. It occurs most commonly in the setting of an underlying coagulopathy, and without treatment, it can lead to hepatocellular necrosis and liver failure.[1]

Noncontrast computed tomography of the abdomen and pelvis revealed a defect within the hepatic vein along with a normal-sized heterogeneous liver, abdominal ascites, and bilateral pleural effusions. Because of the patient's acute kidney injury, a contrast study was not performed, and the vasculature could not be clearly assessed. Viral hepatitis B and C serologies yielded negative results. An acetaminophen level was undetectable.



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**2. Which *one* of the following tests should be performed *next*?**

a. Doppler ultrasonography
b. Liver biopsy
c. Endoscopic retrograde cholangiopancreatography
d. Magnetic resonance imaging
e. Contrast venography

The abnormality detected on computed tomography is suggestive of hepatic vein thrombosis, particularly in this clinical context. Utilization of multiple imaging modalities is appropriate when hepatic vein thrombosis is suspected; however, the initial investigation should consist of Doppler ultrasonography of the liver. This modality provides excellent visualization of the hepatic vasculature, is widely available, and is cost-effective. Liver biopsy is not recommended when acute hepatic vein thrombosis is suspected. Endoscopic retrograde cholangiopancreatography is an invasive procedure that would not provide visualization of the hepatic veins. Magnetic resonance imaging may be useful in defining areas of hepatic necrosis but should not be performed routinely. Lastly, contrast venography is an invasive procedure and is only recommended when the initial imaging findings are nondiagnostic but suspicion for hepatic vein thrombosis remains high. Additionally, contrast venography is associated with contrast-induced nephropathy, and the patient's elevated creatinine level raises concerns about worsening underlying kidney injury.[2,3]

Doppler ultrasonography of the liver revealed no flow in the main and left hepatic veins. The right hepatic vein was poorly visualized. The portal venous system was patent. An intravenous heparin nomogram was initiated. Ultrasound-guided paracentesis was planned.

**3. Which *one* of the following ascitic fluid characteristics is *most suggestive* of this patient's condition?**

a. Polymorphonuclear cell count greater than 250 cells/mm$^3$
b. Ascitic protein level of 2.5 g/dL or higher, serum albumin to ascites gradient (SAAG) of 1.1 g/dL or greater
c. Ascitic protein level of 2.5 g/dL or greater, SAAG less than 1.1 g/dL
d. Ascitic protein level less than 2.5 g/dL, SAAG of 1.1 g/dL or higher
e. Ascitic protein level less than 2.5 g/dL, SAAG less than 1.1 g/dL

Interpretation of ascitic fluid components is an important knowledge concept for clinicians. Basic evaluation of the ascitic fluid includes cell count, total protein level, and albumin concentration. Additional testing such as glucose, lactate dehydrogenase, amylase, cultures, and Gram stain should be considered depending on the clinical scenario. A polymorphonuclear cell count greater than 250 cells/mm$^3$ is suggestive of infection, most commonly spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis largely presents in patients with cirrhosis and ascites. Clinical signs and symptoms can include fever, abdominal pain, and altered mental status. It occurs as portal hypertension leads to transudation of gut bacteria through the bowel into the peritoneum.[4] The SAAG is calculated using serum albumin and ascitic fluid albumin concentrations and delineates whether portal hypertension is present. An SAAG of 1.1 g/dL or greater accurately predicts portal hypertension with 97% accuracy. Along with SAAG, the total protein level is useful in determining the etiology of fluid formation, with a threshold of 2.5 g/dL or higher and less than 2.5 g/dL used to guide the differential diagnosis. An ascites protein level of 2.5 g/dL or higher with an SAAG of 1.1 g/dL or higher is suggestive of portal hypertension coupled with increased hydrostatic pressure. Such a scenario is most commonly due to right-sided heart failure but can also be seen in hepatic venous occlusive disease or Budd-Chiari syndrome, such as this in this case. An ascites protein level of 2.5 g/dL or higher with an SAAG of less than 1.1 g/dL is suggestive of tuberculosis or malignant disease. An ascites protein level of less than 2.5 g/dL with an SAAG of 1.1 g/dL or higher is suggestive of cirrhosis. Lastly, an ascites protein level of less than 2.5 g/dL with an SAAG of less than 1.1 g/dL is suggestive of nephrotic syndrome.[5]

The analysis of the ascitic fluid was suggestive of Budd-Chiari syndrome, with an ascites protein level of 2.5 g/dL or higher and an SAAG of 1.1 g/dL or higher. Cytologic examination revealed no evidence of malignant

disease. Despite 48 hours of anticoagulation, the patient's right upper quadrant abdominal pain persisted.

**4. Which *one* of the following interventions should be performed *next* in the management of this patient's condition?**

a. Continue medical management only
b. Surgical portosystemic shunting
c. Transjugular intrahepatic portosystemic shunt (TIPS)
d. Liver transplant
e. Intravascular thrombolysis

There are many viable treatment options for hepatic vein thrombosis. Clinicians should utilize a stepwise approach to minimize invasive interventions.[6] Medical management consisting of anticoagulation and supportive care may be effective in patients with a mild presentation and incomplete occlusion of hepatic venous outflow. Angioplasty may be considered in patients with thrombosis of only a short segment of vasculature. Surgical portosystemic shunting may be the best option for patients with a subacute presentation and intact liver function when TIPS is not practical or feasible. Placement of a TIPS is effective for acute obstruction and is less invasive than surgical intervention. Liver transplant is appropriate if clinical diagnosis is delayed and progression to fulminant liver failure occurs.[7] Intravascular thrombolysis is rarely utilized.

Because of persistent and marked elevation in liver transaminase levels and prolongation of prothrombin time, a TIPS procedure was successfully performed. Throughout the hospitalization, the patient's hemoglobin level was persistently elevated at more than 18 g/dL. Her erythropoietin level was suppressed.

**5. Which *one* of the following tests should be performed *next* to establish the underlying etiology of the patient's acute presentation?**

a. Flow cytometry
b. *JAK2* genetic testing
c. Bone marrow biopsy
d. Carbon monoxide measurement
e. Polysomnography

The finding of elevated hemoglobin/hematocrit coupled with hepatic venous occlusive disease is suggestive of an underlying hematologic neoplastic process, such as polycythemia vera. Flow cytometry is useful in the work-up of leukocyte abnormalities and may detect paroxysmal nocturnal hemoglobinuria, lymphoma, and leukemia. However, it should not be routinely ordered in the work-up of polycythemia. *JAK2* genetic testing is highly sensitive and specific for polycythemia vera—95% of all cases of polycythemia vera abnormalities are due to the V617F mutation in exon 14 of the *JAK2* gene. If suspicion for polycythemia vera is high, as in this case, *JAK2* genetic testing should be conducted. Bone marrow biopsy should not be performed initially and should be considered only after consultation with a hematologist. Measuring the carbon monoxide level would not be helpful because there is no historical context to suggest carbon monoxide poisoning in this patient. Polysomnography may be indicated if sleep apnea is suspected clinically and initial work-up indicates secondary polycythemia.[8,9]

*JAK2* testing was performed and was positive for genetic mutation. Subsequently, bone marrow biopsy confirmed the diagnosis of polycythemia vera. Within 2 weeks of TIPS placement, results of liver enzyme and function tests normalized, and ascites resolved. Hematology and oncology services were consulted after hospital dismissal, and hydroxyurea was initiated for treatment of polycythemia vera. At last follow-up, the patient was doing well.

## DISCUSSION

Budd-Chiari syndrome is a life-threatening condition that occurs with occlusion of the hepatic venous outflow. In this case, Budd-Chiari syndrome was first suspected clinically because of the patient's abdominal pain, acute development of ascites, and severe derangements in liver function test results.[10] The differential diagnosis for hepatocellular liver injury with liver transaminase levels greater than 1000 U/L is quite limited. Other than Budd-Chiari syndrome, possible etiologies include ischemic hepatitis, drug-induced liver injury (eg, acetaminophen hepatotoxicity), and acute viral hepatitis. Uncommonly, autoimmune hepatitis and acute biliary obstruction will elevate liver transaminase levels to more than 1000 U/L. Ischemic hepatitis, also known as shock liver or hypoxic hepatitis, occurs when there is decreased blood flow to the liver


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parenchyma and often is seen in patients with concomitant passive congestion of the liver due to heart failure. It is most commonly seen in the setting of hypotension, as with hemorrhagic shock from trauma or cardiogenic shock from myocardial infarction. Liver function will typically recover once perfusion is restored. Acetaminophen hepatotoxicity occurs after either intentional or inadvertent ingestion of large amounts of acetaminophen and can lead to liver failure if not promptly identified and treated. Viral hepatitis, especially herpes simplex virus hepatitis, can lead to extensive hepatocellular necrosis and striking elevations in liver transaminase levels.[1]

Budd-Chiari syndrome most commonly occurs as the result of hepatic vein thrombosis that leads to hepatic congestion and subsequent ischemic necrosis. Because of this association, the terms *hepatic vein thrombosis* and *Budd-Chiari syndrome* are often used interchangeably. It is critical that the Budd-Chiari syndrome be recognized promptly so that appropriate and definitive therapies are initiated.

Budd-Chiari syndrome is considered primary when hepatic venous outflow obstruction occurs as a result of vascular pathology and is considered secondary when there is extrinsic compression or occlusion of the vasculature from another cause. The acuity and severity of clinical presentation can vary substantially. Patients experiencing sudden occlusion of venous outflow are more likely to be symptomatic (abdominal pain, systemic illness) and have development of acute hepatitis and liver failure. Patients who have slowly progressive venous outflow occlusion may be entirely asymptomatic until they eventually have development of lower extremity edema and ascites secondary to portal hypertension.[7]

In most cases, the etiology of hepatic vein thrombosis can be identified. Potential etiologies include hypercoagulable states, obstructive lesions (infectious, benign, neoplastic), and a variety of systemic disorders. Inciting hypercoagulable states are numerous and include myeloproliferative disease (such as polycythemia vera and essential thrombocytosis), oral contraceptive treatment (especially with concomitant smoking), pregnancy, heparin-induced thrombocytopenia, factor V Leiden disorder, antithrombin III deficiency, protein C or S deficiency, prothrombin gene mutation, antiphospholipid syndrome, and paroxysmal nocturnal hemoglobinuria. Infection can cause venous outflow obstruction when a liver abscess compresses the vasculature. Additionally, invasive aspergillosis and mucormycosis can directly invade the hepatic venous outflow tract. Benign lesions such hepatic cysts and adenomas can compress hepatic outflow by mass effect. A variety of solid tumor malignancies can cause similar compression, with hepatocellular carcinoma being the most common. Associated systemic disorders include (but are not limited to) Behçet disease, inflammatory bowel disease, systemic lupus erythematous, Sjögren syndrome, hypereosinophilia syndrome, and $\alpha_1$-antitrypsin deficiency.[7]

Diagnosis of Budd-Chiari syndrome is accomplished utilizing various forms of abdominal and vascular imaging. Doppler ultrasonography of the liver provides excellent visualization of the hepatic vasculature, is widely available, and is cost-effective. Contrast-enhanced computed tomography and magnetic resonance imaging are useful in defining areas of hepatic necrosis. Contrast venography can be utilized when the initial imaging findings are nondiagnostic but suspicion for hepatic vein thrombosis remains high. Following diagnosis, further work-up to identify the underlying etiology should be initiated on the basis of the clinical presentation.[3]

Without treatment, Budd-Chiari syndrome can lead to substantial morbidity and mortality. Anticoagulation and supportive care should be initiated immediately once the diagnosis has been made to prevent clot propagation. In patients with intact liver function, attempts should be made to restore patency of the hepatic vasculature and relieve liver congestion. This goal can be accomplished with TIPS placement, surgical portosystemic shunting, or angiography with intravascular thrombolysis or thrombectomy. Selection of the appropriate intervention depends on clinical presentation, patient anatomy, and institutional resources. Expert consultation should be sought once intervention is deemed necessary. In patients with fulminant liver failure or cirrhosis, management should focus on preventing complications and treating symptoms while initiating consideration for liver transplant.

In summary, this patient had primary Budd-Chiari syndrome occurring secondary to

polycythemia vera, which is the most common identifiable cause of this syndrome. The diagnosis was established with use of a combination of vascular ultrasonography and contrast-enhanced computed tomography. Identification of the underlying etiology as polycythemia vera was accomplished by measurement of erythropoietin levels, *JAK2* genetic testing, and eventually a bone marrow biopsy. Therapeutic anticoagulation and prompt intervention with TIPS led to an excellent outcome.

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



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