59-Year-Old Man With Fever and Abdominal Pain

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A 59-year-old man presented to the emergency department with a 24-hour history of postprandial epigastric abdominal pain, chills, rigors, and a fever of 38.9 °C (102.02 °F). Past medical history was significant for Crohn disease, asthma, hypertension, and cholecystectomy 3 weeks before, secondary to acute necrotizing and hemorrhagic cholecystitis. Upon presentation, the patient denied any associated nausea, vomiting, constipation, diarrhea, hematochezia, or melena.

Physical examination revealed an obese man with body mass index (BMI) of 34.0 kg/m^2. The patient was afebrile and oriented to time, place, and person. Cardiopulmonary examination results were unremarkable. The abdomen was soft, with notable epigastric tenderness to palpation but no peritoneal signs. Bowel sounds were present. There was no overt hepatosplenomegaly or shifting dullness present. Rectal examination results were benign without fissures or hemorrhoids. Neurologic, skin, and extremity examination results were within normal limits. Mild scleral icterus was present.

Initial laboratory results revealed the following (reference ranges provided parenthetically): hemoglobin, 13.5 g/dL (13.5 to 17.5 g/dL) with a mean corpuscular volume of 92.7 fL (81.2 to 95.1 fL); leukocytes, 11.3 x 10^9/L (3.5 to 10.5 x 10^9/L); platelet count, 298 x 10^9/L (150 to 450 x 10^9/L); sodium, 137 mmol/L (135 to 145 mmol/L); potassium, 3.6 mmol/L (3.6 to 5.2 mmol/L); alkaline phosphatase (ALP), 248 U/L (45 to 115 U/L); aspartate aminotransferase (AST), 196 U/L (8 to 48 U/L); alanine aminotransferase (ALT), 239 U/L (7 to 55 U/L); total bilirubin, 4.5 mg/dL (≤1.2 mg/dL); direct bilirubin, 3.4 mg/dL (0.0 to 0.3 mg/dL); creatinine, 0.9 mg/dL (0.8 to 1.3 mg/dL); serum urea nitrogen, 15 mg/dL (8 to 24 mg/dL); lactate, 1.0 mmol/L (0.6 to 2.3 mmol/L); and lipase, 27 U/L (10 to 73 U/L). The patient was vitally stable with a blood pressure of 148/78, heart rate of 88, oxygen saturation of 95% on room air, and a temperature of 37.4 °C (99.32 °F).

1. **Which of the following physical examination findings, if present, would *most likely* be associated with a worse prognosis in this patient upon presentation?**
   a. Abdominal pain
   b. Scleral icterus
   c. Fever
   d. Jaundice
   e. Confusion

Charcot triad (fever, abdominal pain, and jaundice) is widely used as diagnostic criteria for acute cholangitis. However, it has low sensitivity (26.4%) in the setting of high specificity (95.9%).[1] Fever is noted in 95% of patients and is commonly greater than 39 °C (102.2 °F). Right upper-quadrant pain is found in 90% of patients, but jaundice (80%) and peritoneal signs (15%) are found less often. Charcot triad, along with altered mental status and hypotension, is known as Reynold pentad and is indicative of Gram-negative septicemia.[2]

In 2007, the Tokyo Guidelines were developed to standardize the diagnostic criteria and for assessment of severity of acute cholangitis. The revised Tokyo Guidelines (TG13) have sensitivity of 91.8% and specificity of 77.7%. Diagnostic criteria include systemic inflammation, cholestasis, and imaging findings. Systemic inflammation is defined by fever or increased inflammatory

See end of article for correct answers to questions.

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response, suggested by an abnormal white blood cell count (WBC) or increase in C-reactive protein. Cholestasis is suggested by jaundice or elevation in liver tests (AST, ALT, ALP, and gamma-glutamyl transferase [GGT]) that is 1.5 times the upper limit of normal. Imaging findings supportive of cholangitis include biliary dilatation, stricture, or stone. A suspected diagnosis includes an item from the systemic inflammation category plus 1 from the cholestasis or the imaging category. A definitive diagnosis includes an item from each category.[1]

The severity assessment of cholangitis is based on signs of organ dysfunction and 5 factors deemed predictive of a poor prognosis. Grade III severe acute cholangitis is defined as cholangitis that is associated with the onset of dysfunction in at least 1 organ system. This can be cardiovascular (hypotension requiring dopamine ≥5 μg/kg per minute, or any dose of norepinephrine), neurologic (disturbance of consciousness), respiratory dysfunction (PaO2/FiO2 ratio < 300), renal dysfunction (oliguria, serum creatinine >2.0 mg/dL), hepatic dysfunction (prothrombin time and international normalized ratio [PT/INR] >1.5) or hematologic dysfunction (platelet count <100,000/mm^3). Grade II moderate acute cholangitis is associated with any 2 of the following conditions that are deemed predictive of a poor prognosis. They include an abnormal WBC count (>12,000/mm^3, <4000/mm^3), high fever (≥39 °C [102.2 °F]), age (≥75 years), hyperbilirubinemia (total bilirubin ≥5 mg/dL), and hypoalbuminemia (< 70% lower limit of normal). Grade I mild acute cholangitis is defined as anything that does not meet the criteria for Grade III or Grade II.[1]

Abdominal pain is not used to predict prognosis in the Tokyo Criteria. Scleral icterus, fever, and jaundice can qualify as Grade II acute cholangitis if the temperature and total bilirubin levels are high enough. Confusion would qualify as organ dysfunction and therefore be Grade III acute cholangitis.

An abdominal computed tomography (CT) was performed in the emergency department, which revealed a moderate-sized fluid collection (4.8 cm) in the gallbladder fossa, with adjacent inflammatory stranding in the mesenteric fat, and common bile duct dilation to 11 mm. Blood cultures were obtained, and the patient was started on vancomycin and piperacillin-tazobactam before being admitted to the hospital.

2. **In view of the findings on clinical examination, which *one* of the following is the *most appropriate* next step in the management of this patient?**
   a. Heptatobiliary iminodiacetic acid (HIDA) scan
   b. Magnetic resonance cholangiopancreatography (MRCP)
   c. Endoscopic retrograde cholangiopancreatography (ERCP)
   d. Intraoperative cholangiogram
   e. CT-guided percutaneous drainage of the collection

A HIDA scan and MRCP are appropriate options to localize the site of the bile leak but would not offer a therapeutic opportunity. The next best step in the management of this patient would be ERCP, as the patient likely has a bile duct leak as indicated by the CT scan; ERCP would be both diagnostic and therapeutic with potential for sphincterotomy and transpapillary stent placement. Intraoperative cholangiogram would not be an appropriate option, as surgery is not indicated. Percutaneous drainage may be required if persistent or symptomatic biloma occurs after therapeutic ERCP, but rapid reabsorption is expected in most cases after endoscopic closure of the leak, even with large collections.

An ERCP was performed <24 hours into admission and revealed multiple areas of bile-duct stenosis, intermixed with areas of normal and dilated bile ducts, and a minimal cystic duct-bile leak. Multiple strictures were balloon dilated and brushed for cytology. One biliary stent was placed in the right hepatic duct and another in the common bile duct. A sphincterotomy was also performed.

Common complications after cholecystectomy include bleeding, abscess, bile leak, bile-duct injury, and bowel injury.[3] Bile-duct

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injuries are categorized based on the location of injury and are usually identified in the postoperative period rather than intraoperatively. If bile-duct injury is thought to occur during laparoscopic cholecystectomy, conversion to an open procedure with cholangiography is performed to determine further treatment options. Postoperatively, bile-duct injury presents with abdominal pain, fever, and jaundice. Imaging is pertinent to assess for integrity of the biliary tree and for a possible fluid collection. Treatment consists of parenteral antibiotics to cover health care-associated intra-abdominal infection and repair of the injury endoscopically, percutaneously, or with surgery.[4]

Bile-duct leaks present similarly with fever, abdominal pain, and jaundice. Leakage occurs from the intervened upon cystic duct or ducts of Luschka. Patients typically present in the week following cholecystectomy and should have CTs performed on presentation. The CT scan often shows a fluid collection in the right upper quadrant or ascites. If imaging indicates that the leak is from the cystic duct stump, stenting of the common bile duct and transpapillary sphincterotomy is performed to decrease pressure of the proximal biliary system and prevent further leakage.[4]

The patient returned to the hospital and was observed for 24 hours postprocedure. The cytology of the multiple bile-duct stenoses that were intermixed with areas of normal and dilated bile ducts was ultimately negative for malignancy.

3. **Which *one* of the following is the *most likely* additional diagnosis suggested by the ERCP findings?**

   a. Choledocolithiasis
   b. Primary biliary cholangitis
   c. Primary sclerosing cholangitis (PSC)
   d. Cholangiocarcinoma
   e. Caroli disease

The description is not suggestive of choledocholithiasis, as this would show stones within the bile duct that appear as filling defects with upstream dilation of the bile duct. Primary biliary cholangitis does not present with intra- or extrahepatic biliary abnormalities on cholangiogram but rather with histologic evidence of interlobular bile duct injury.[2] The cholangiogram findings are suggestive of PSC. The diagnosis of PSC is made when these characteristic findings are found on imaging, along with consistent clinical, serologic, and histologic findings. Secondary causes of sclerosing cholangitis must also be ruled out, including choledocholithiasis, chronic bacterial cholangitis, cholangiocarcinoma, and Caroli disease.[2] Cholangiocarcinoma is not the most likely diagnosis, as there is no evidence of a mass or dominant stricture suggesting a malignant process. Caroli disease is a congenital disease of the segmental intrahepatic bile ducts.[2] It results in irregular dilations of the larger intrahepatic bile ducts, which is not evident in the description given earlier.

The patient was diagnosed with postcholecystectomy small bile-duct leak and background PSC.

4. **Which *one* of the following is the *most appropriate* treatment for PSC?**

   a. Supportive treatment
   b. Ursodeoxycholic acid
   c. Prednisone
   d. Infliximab
   e. Colchicine

No definitive treatment has demonstrated to be effective for PSC aside from liver transplantation, so supportive treatment is the best answer. A large number of medications have been trialed, but none has been shown to undoubtedly change the course of PSC.[2] Ursodeoxycholic acid is the best studied drug in PSC. It was shown to partially improve serum liver biochemistry levels in several trials but did not demonstrate a survival benefit or delay in progression of disease and the need for liver transplantation.[5] Higher doses of ursodeoxycholic acid were tested in a prospective placebo-controlled randomized trial but showed increased risk of death, need for liver transplantation, and progression of varices.[6] Prednisone,[7] infliximab,[8] and colchicine[9] have not demonstrated significant benefit in the treatment of PSC.

The patient was able to tolerate an oral diet and was vitally stable, with improving laboratory values including liver enzymes. He was discharged with a 10-day course of oral antibiotics and close follow-up.

5. **In the outpatient setting, which *one* of the following is the *most appropriate* next step in cancer screening for this patient?**
   a. Carbohydrate antigen 19-9 (CA 19-9) annually
   b. MRCP annually
   c. Colonoscopy annually
   d. Abdominal ultrasound annually
   e. ERCP annually

Patients with PSC will usually undergo screening for cholangiocarcinoma and gallbladder carcinoma, in addition to age-appropriate cancer screening, because of increased risk of these cancers.[2] Guidelines for cancer surveillance in patients with PSC are presented from a number of different expert groups, but there is no clear agreement on the best strategy. The effectiveness of screening with CA 19-9 and MRCP for cholangiocarcinoma and gallbladder carcinoma has yet to be proved.[10,11] On the other hand, the risk of colorectal dysplasia in patients with PSC and ulcerative colitis is higher than those with ulcerative colitis alone.[12] It is therefore recommended that patients with inflammatory bowel disease have colonoscopies annually after the diagnosis of PSC.[10] Colonoscopy annually would therefore be the best answer, as our patient has a history of Crohn disease. The effectiveness of screening with abdominal ultrasound and ERCP for cholangiocarcinoma and gallbladder carcinoma has yet to be proved.[10,11]

The patient was subsequently hospitalized several times for recurrent ascending cholangitis and a hepatic abscess. He was followed closely with liver chemistries and CA 19-9 every 6 months. Abdominal ultrasound or MRCP was obtained yearly to screen for cholangiocarcinoma. Because the patient had multiple episodes of ascending cholangitis, with several leading to bloodstream infections, he was started on suppressive antibiotics. He experienced an episode of recurrent C. difficile infection, requiring hospitalization, while on suppressive antibiotics, so he was evaluated and ultimately listed for a liver transplant. The patient has maintained his quality of life and has not experienced sequelae of portal hypertension, so he continues to have close follow-up with the liver-transplant team.

DISCUSSION

This case highlights the importance of early recognition of cholangitis and postcholecystectomy complications and the diagnostic importance of basic laboratory testing, imaging, and physical examination in patients with suspected cholangitis. The Tokyo Guidelines provide a standardized framework for diagnosing and assessing the severity of patients with acute cholangitis. The gold standard remains ERCP for diagnosing and treating acute cholangitis and bile leak when there is a high pretest probability. Other diagnostic and intervention modalities, such as MRCP, intraoperative cholangiogram, and CT-guided percutaneous drainage, may be indicated based on the clinical context. Bile-duct injuries and leaks can be seen commonly after cholecystectomy and present with fever, abdominal pain, and jaundice. Imaging is imperative to localize the source of bile leakage and to tailor treatment.

Primary sclerosis cholangitis is an idiopathic, chronic, progressive disorder that results in patchy inflammation, fibrosis, and destruction of intrahepatic and extrahepatic biliary tracts. It is diagnosed based on characteristic imaging, history, and laboratory values in addition to exclusion of secondary causes. No definitive treatment for PSC has demonstrated to be effective except for liver transplantation. Proper screening in the outpatient setting is imperative, as patients are at increased risk of cholangiocarcinoma, hepatocellular carcinoma, gallbladder carcinoma, and colon cancer. Colon cancer screening is the only preventive strategy that has proved effective in patients with PSC. Abdominal ultrasound, MRCP, and CA 19-9 may be indicated on a routine basis to monitor for cancers of the liver, gallbladder, and biliary tract, but no

studies have been performed to demonstrate benefit as screening tests. There are ongoing clinical trials assessing the benefit of alternative treatments for PSC, including oral vancomycin (phase 3-NCT01802073) and nor-ursodeoxycholic acid (phase 2-NCT017 55507). Liver transplant remains the main treatment for patients with decompensated cirrhosis secondary to PSC.[10] Until new therapies are available for the treatment of PSC, early diagnosis and surveillance for complications are crucial in improving PSC outcomes.

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