Clinical Problem-Solving

This Clinical Problem-Solving case is based on a presentation at the Beth Israel Deaconess Medical Center Morbidity and Mortality Conference.

Chest Pain with a Surprising Course

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A 73-year-old man with insulin-dependent diabetes mellitus and a history of coronary artery disease came to the emergency department because of chest pain of one hour's duration that radiated to the jaw and back, shortness of breath, diaphoresis, and a nonproductive cough. The pain was similar to the angina he usually experienced, except for an intermittent pleuritic component with accompanying discomfort on the right side of the chest. An electrocardiogram showed right bundle-branch block with T-wave inversion in leads V_1 through V_4, but an electrocardiogram obtained 11 days earlier showed the same findings. The patient was admitted to the hospital.

Eleven days earlier, the patient had been hospitalized for three days after experiencing intermittent substernal chest pain radiating to the back, accompanied by nausea and vomiting, for 10 hours. Cardiac catheterization performed at that time showed severe, three-vessel coronary disease in the patient's native coronary arteries. The saphenous-vein grafts and left-internal-mammary-artery graft that had been placed during coronary-artery bypass surgery five years earlier were patent. The patient underwent successful rotational atherectomy of the left anterior descending artery and the first diagonal vessel. After angioplasty, the chest pain and nausea had resolved. Myocardial infarction was ruled out at that time on the basis of serial measurements of creatine kinase.

A Cardiologist: The patient may have had a myocardial infarction. Patients with prior coronary bypass grafting usually do not have marked electrocardiographic changes during an infarction. About 10 to 15 percent of vein grafts are no longer functional 1 month after coronary-artery bypass grafting, and another 10 percent fail 2 to 12 months after surgery, with a subsequent failure rate of about 1 to 2 percent per year. After five years, the cumulative loss is approximately 30 to 35 percent. Complications 10 days after a coronary intervention are unusual, but they could be due to a delayed abrupt closure of a coronary artery.

The patient was taking pentoxifylline and ibuprofen. He had had malaise and nausea two days earlier and an episode of vague abdominal discomfort and emesis on the day of admission. He had no fever, headache, sputum production, hemoptysis, hematemesis, diarrhea, or dysuria. He was treated for unstable angina with aspirin, intravenous nitroglycerin, heparin, and intravenous morphine, with complete resolution of the chest pain. The blood pressure was 142/58 mm Hg, the pulse was 85, the respirations were 15, the temperature was 35.7°C, and the oxygen saturation was 96 percent when the patient was receiving 2 liters of oxygen by nasal cannula. The patient was sitting but was in mild distress and was diaphoretic. The jugular venous pressure was less than 10 cm; the lungs had bibasilar rales. The heart and abdominal examinations were unremarkable. The rectal examination showed brown stool, and a test for occult blood was negative. The remainder of the physical examination was normal. The white-cell count was 39,000 per cubic millimeter, and the hematocrit was 33.1 percent. The differential count was 90 percent neutrophils, 6 percent bands, 2 percent lymphocytes, and 2 percent monocytes. The urea nitrogen concentration was 13 mg per deciliter (4.6 mmol per liter), and the creatinine concentration was 0.9 mg per deciliter (79.6 μmol per liter). Urinalysis showed a glucose concentration of more than 1000 mg per deciliter (55.5 mmol per liter) and ketones (40 mg per deciliter). The chest radiograph showed moderate left ventricular enlargement, a slightly elevated left hemidiaphragm, bilateral small pleural effusions, and a wedge-shaped infiltrate in the posterior basal segment of the left lower lobe, with some volume loss.

An Internist: The electrocardiographic findings do not suggest acute ischemia, so other causes of pain and diaphoresis, such as an infection, should be

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considered. The infiltrate seen on the radiograph is not very impressive and is not necessarily the source of the infection.

AN INFECTIOUS-DISEASE PHYSICIAN: Two things are disturbing. First, the patient described chest pain radiating to his back, which is not typical of coronary-artery pain. Second, the white-cell count is abnormal, even in the absence of fever. The wedge-shaped infiltrate on the lateral chest film might be the consequence of an occult focus of infection, such as vertebral osteomyelitis or endocarditis. Other possibilities include aspiration pneumonia and an early stage of community-acquired pneumonia. I would certainly order blood cultures, review the previous angiographic studies for evidence of emboli to the coronary arteries, and order echocardiographic studies. I would also obtain better views of the spine. Since the left diaphragm is elevated on the chest film, there may be fluid under it. I would also want to see a computed tomographic (CT) scan.

Although the patient is afebrile, the temperature of 35.7°C could be a sign of sepsis, especially given his age. His hemodynamic status is stable, but he may have an occult source of bacteremia. He is also receiving two drugs that have major effects on temperature regulation.

The patient was admitted to the cardiac care unit. Treatment with intravenous cefuroxime was started for possible pneumonia. Four hours after admission, his temperature rose to 38.9°C, and he had chills, rigors, and emesis. Mild jaundice was noted. Liver-function tests on a blood sample obtained at admission showed the following values: alanine aminotransferase, 171 U per liter; aspartate aminotransferase, 251 U per liter; alkaline phosphatase, 260 U per liter; lactate dehydrogenase, 698 U per liter; and total bilirubin, 6.2 mg per deciliter (106.0 μmol per liter). Cefuroxime was discontinued, and treatment with ampicillin, gentamicin, and metronidazole was begun.

A GASTROENTEROLOGIST: Since the values for alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase are all elevated, prehepatic reabsorption of blood from a hematoma is unlikely, as is intrahepatic jaundice due to drug-related hepatitis, viral hepatitis, or another liver disorder. That leaves posthepatic jaundice, with causes such as pancreatitis and a common-bile-duct stone stricture. In this patient, the likelihood of ascending cholangitis is very high.

Jaundice is considered an emergency in adults only if the cause is ascending cholangitis, fulminant hepatic failure, or massive hemolysis. With massive hemolysis, the emergency is due not to the level of bilirubin itself but to the disease causing the hemolysis, such as falciparum malaria, blackwater fever, or clostridium sepsis.[1] Because the patient has diabetes and is elderly, I would order ultrasound studies to rule out a distended biliary tree, an abnormal gallbladder, and gallstones. A liver abscess is unlikely, given the rapid course of the illness. If the ultrasound studies did not provide an answer, I would obtain a CT scan.

The patient was probably jaundiced on admission. The elevated lactate dehydrogenase level could have an extrahepatic source; he could have hemolysis with sepsis and disseminated intravascular coagulation. Is this an emergency in which the patient has ascending cholangitis with pus in the bile duct that needs to be drained? An obstructed common duct could explain his earlier symptoms.

The patient's urine output fell to 200 ml in eight hours, and diarrhea developed. The urine sediment contained renal tubular cells, few red cells, and no casts. The patient's hemodynamic status remained stable, with little change in the findings on physical examination except for the jaundice. Studies of a blood specimen obtained eight hours after admission showed a drop in the hematocrit, from 33 percent to 15 percent, and further elevations in liver-function values: alanine aminotransferase, 464 U per liter; aspartate aminotransferase, 894 U per liter; alkaline phosphatase, 489 U per liter; lactate dehydrogenase, 3430 U per liter; and total bilirubin, 13.8 mg per deciliter (236.0 μmol per liter). The serum creatinine concentration rose to 1.7 mg per deciliter (150.3 μmol per liter), the potassium concentration rose to 4.8 mmol per liter, and the bicarbonate concentration fell from 22 mmol per liter at admission to 14 mmol per liter. A direct Coombs' test was negative on admission but was weakly positive for IgG and complement 13 hours later.

A peripheral-blood smear showed a markedly elevated leukocyte count, with many neutrophils, a striking number of spherocytes, and small particles that might have been platelets, red-cell fragments, or microspherocytes. The neutrophils looked vacuolated and somewhat hypogranulated.

A HEMATOLOGIST: Since there is no evidence of gastrointestinal bleeding and sepsis is suspected, the rapid fall in the hematocrit may be due to hemolysis. Is this a fragmentation hemolysis as in disseminated intravascular coagulation or a spherocytic hemolysis related to a progressive underlying condition? The direct Coombs' test can be nonspecific. A unifying diagnosis would be intravascular hemolysis caused by infection and resulting in microspherocytic hemolytic anemia. What organism typically causes intravascular hemolysis? Clostridium.[2] Leptospirosis can lead to a spherocytic hemolytic anemia, but not as rapidly as

clostridial infection can. Infections that affect red cells, such as malaria, amebiasis, bartonellosis, and brucellosis, can cause hemolytic anemia, but again, not rapidly. No therapeutic drug that I know of can cause such a brisk, dramatic hemolysis. Chemicals and toxins can do so, but the patient does not have a history of such exposure. I think he has sepsis.

A NEPHROLOGIST: Sepsis makes it difficult to determine the nature of the renal failure. Hemodynamic factors can cause acute tubular necrosis in patients with prerenal failure, even with a high cardiac output, and patients with intravascular hemolysis can have hemoglobinuric renal failure.

The working diagnosis of the hematology consultant was hapten-mediated autoimmune hemolysis related to treatment with cefuroxime.

AN INFECTIOUS-DISEASE PHYSICIAN: I disagree. Treatment with cephalosporins often results in a positive Coombs' test but almost never causes hemolysis. Ampicillin is a much more likely culprit, especially if the patient had prior exposure to it. The suggestion of clostridial sepsis is very interesting. With this condition, you often see massive hemoglobinuria — the blood itself can be tinged with hemoglobin. The key question is: What is the source of the clostridial sepsis? Usually, it occurs in patients with gastrointestinal tumors who have bacteremia with strains of clostridium other than *Clostridium perfringens.*

Consultants on the renal service thought the patient had anuric renal failure due to massive hemolysis. Since the patient already had anuria, they thought it was too late to administer fluids and alkalinize the urine in order to treat pigment-induced acute tubular necrosis. They made the point that the hemoglobin molecule is too large to dialyze and recommended supportive care and adjustment of all medications for the lack of kidney function. By about 14 hours after admission, blood cultures were growing gram-positive rods in three of four bottles. Consultants on the infectious-disease service saw the patient.

AN INFECTIOUS-DISEASE PHYSICIAN: Clostridial infection is clearly the most likely diagnosis. Corynebacterium, other diphtheroids, and other gram-positive rods do not cause this syndrome. Bacillus species, which we see occasionally in drug addicts and immunocompromised patients, do not cause hemolysis either. Infection with *C. perfringens* is highly unlikely because there is no known source. The patient does not have gas gangrene. Although he could have an intraabdominal abscess, this sort of spontaneous bacteremia is usually associated with *C. septicum, C. sordellii,* or one of the strains that occur with gastrointestinal tumors. Bowel perforation may be the cause of the pulmonary infiltrate and elevated diaphragm. Clostridia often establish infection elsewhere outside the bloodstream, so it is important to watch for crepitant cellulitis in the skin, myonecrosis of muscles anywhere in the body, or reports of severe pain. Penicillin is the drug of choice, but it could be the cause of the hemolysis. The role of clostridial antitoxin in this setting is uncertain.

In elderly patients, positive blood cultures for clostridium species, especially *C. perfringens,* are not uncommon. Most elderly patients with positive cultures are not sick. When the clostridia are confined to the bloodstream, they do not release toxins. They need an anaerobic environment, such as necrotic tissue, to release toxins, which in turn cause a fulminant syndrome. It is important to look for the source, which is generally in the abdomen. In this diabetic patient with abnormal liver-function results, the gallbladder is another likely site.[3,4]

The infectious-disease consultants thought that the patient had clostridial sepsis due to a gastrointestinal lesion in the gallbladder or the colon. They recommended treatment with intravenous penicillin, clindamycin, and ceftriaxone and abdominal imaging.

The diarrhea persisted and shortness of breath, intermittent nausea, vomiting, and pain in the right upper quadrant developed 16 hours after admission. The patient was transferred to the intensive care unit for dialysis. Abdominal ultrasound studies were limited because bowel gas in the right upper quadrant obscured the gallbladder and porta hepatis. With allowance for this limitation, echogenic foci in the portal vein on real-time imaging were thought to be suggestive of portal venous gas. A CT scan, obtained to rule out bowel ischemia (Fig. 1), showed an unusual collection of gas overlying the lower part of the liver and very little gas in the bowels. The cross-sectional images showed gas in the gallbladder and the gallbladder wall, permeating the surrounding liver parenchyma, and probably in the tributary biliary ducts. No gallstones were seen.

A SURGEON: Surgery is indicated immediately. Ideally, it should have been done sooner. The patient has diabetes, he has clostridia in his blood, and now he has emphysematous cholecystitis. Percutaneous drainage is not a realistic option. He has a necrotic process that needs to be extirpated. Even in the less dramatic situation of acalculous cholecystitis, which is probably what led to the patient's current condition, percutaneous drainage often fails, because the problem is an infected gallbladder wall, not a stone impacted in the cystic duct, with infected bile.[5] Clostridial sepsis is associated with a very high mortality rate, whatever the course.

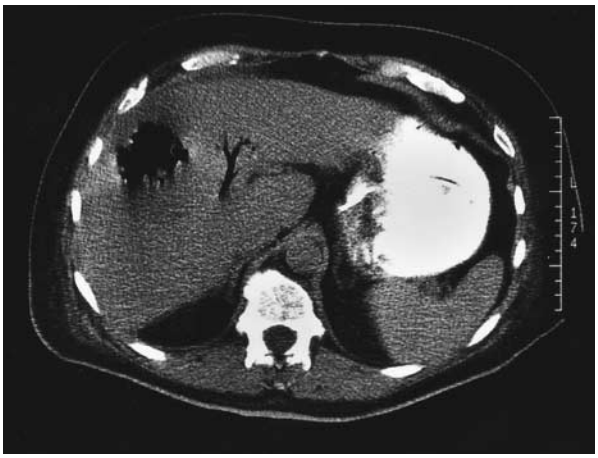

Figure 1. CT Scan of the Abdomen.
There is an abnormal air density within the gallbladder fossa and the gallbladder wall, with associated pneumobilia. The findings are consistent with the presence of emphysematous cholecystitis and cholangitis.

The patient was taken to the operating room 18 hours after admission, where he was found to have a friable, perforated gallbladder. Cholecystectomy was performed. The gallbladder was grossly necrotic, the serosa was green, and the surface had multiple areas of white exudate. The tissue was very friable, with little grossly identifiable mucosa. Gram's stain of the bile revealed gram-positive and gram-negative rods. The low-power view of the gallbladder wall (Fig. 2A) showed transluminal necrosis. Brown–Brenn staining showed gram-positive rods in the gallbladder wall (Fig. 2B).

Postoperatively, the patient underwent hemodialysis. On the third hospital day, *C. perfringens* was identified in three of the four original blood-culture bottles, and *Escherichia coli* was identified in two bottles.

The patient was extubated on the fourth hospital day. He was lethargic and unable to follow commands, but he responded to voices by opening his eyes and moaning. He had no focal findings on neurologic examination. His mental status gradually improved with dialysis and improvement of his liver function. Antibiotics were discontinued on the 16th hospital day. Anuria persisted, and the patient was dependent on dialysis. He was thought to have severe acute tubular necrosis. He was discharged to a rehabilitation facility on the 17th hospital day.

The patient's renal function gradually improved, and dialysis was discontinued six weeks after discharge. Five months after the cessation of therapy, he had a creatinine concentration between 1.0 and 1.2 mg per deciliter (88.4 and 106.1 μmol per liter) and was feeling well.

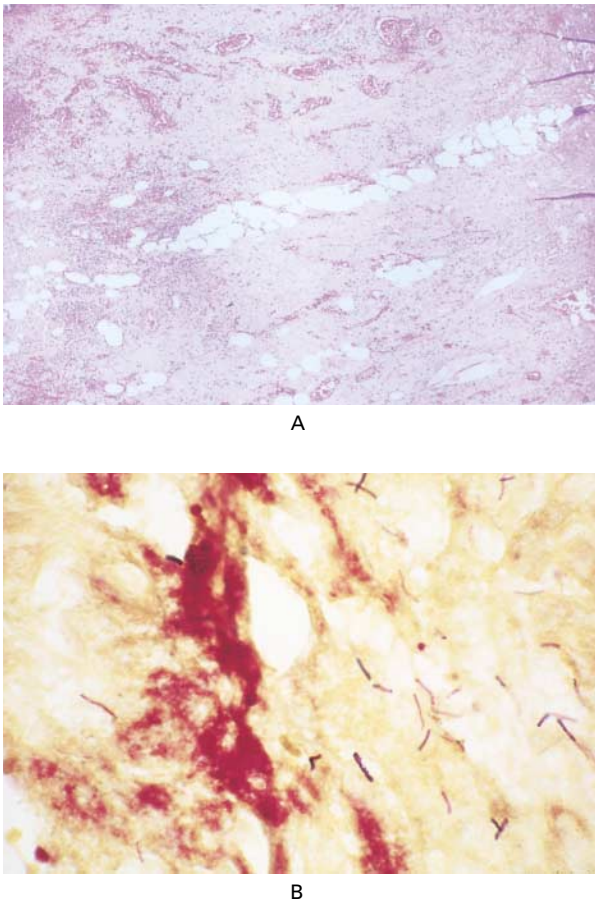

Figure 2. Pathological Findings in the Gallbladder Wall.
Panel A shows transluminal necrosis (hematoxylin and eosin, ×10). Panel B shows gram-positive rods (Brown–Brenn stain, ×40).

The editors asked Joseph Loscalzo, M.D., Ph.D., chairman of the department of medicine at Boston University School of Medicine, to comment on the case.

COMMENTARY

This case illustrates several important points about the care of patients with diabetes who have chest pain and about the infectious complications of diabetes mellitus. Diabetic patients with myocardial ischemia often have atypical presentations, and they are more likely to have silent infarctions than are nondiabetic patients. For this reason, it is important to have a low threshold for diagnosing a probable acute coronary syndrome whenever a patient with diabetes presents with chest discomfort that is visceral — even if atypical — with or without electrocardiographic changes. In this case, the patient also had a history of coronary artery disease, which lowers the diagnostic threshold even further.

The unusual features of this patient's presentation that should have suggested a different diagnosis were

the 11-day history of pain without electrocardiographic changes and the nature of the pain. If the patient had had active myocardial ischemia at rest for 11 days and had presented with pain, one would have expected to find electrocardiographic changes consistent with the presence of ischemia or infarction, echocardiographic wall-motion abnormalities, or both. The presence of trifascicular block on the electrocardiogram does not militate against the diagnosis of an acute coronary syndrome, since the initial depolarization forces in right bundle-branch block are normal. The electrocardiogram, however, is an insensitive tool for diagnosing myocardial ischemia.

Radiation of the pain to the back is also a somewhat atypical symptom of myocardial ischemia, and the patient's comment during the second admission that the chest discomfort at that time was similar to his anginal pain implies that the discomfort during the first admission was not reminiscent of his angina. It is puzzling that the patient was treated with atherectomy of the left anterior descending and first diagonal arteries in the setting of entirely patent bypass grafts, without any assessment of the functional importance of these native coronary lesions. The patient's presenting symptoms at the time of the second admission, although suggestive of angina, were somewhat atypical because of the right-sided pleuritic pain. We subsequently learn that these symptoms — and probably the initial clinical manifestations — were caused by acalculous cholecystitis that progressed to emphysematous cholecystitis complicated by clostridial sepsis and intravascular hemolysis.

The link between the perception of visceral pain and the associated gastrointestinal symptoms of nausea and vomiting is well established for acute myocardial infarction, particularly inferior myocardial infarction. Owing to the risk of myocardial infarction and its complications, especially in patients with diabetes, patients presenting with chest pain and these associated symptoms should always be considered to have an acute coronary syndrome until it has been proved otherwise. However, acute cholecystitis and related hepatobiliary disorders can also mimic an acute myocardial infarction, and can do so in terms of presenting symptoms, electrocardiographic changes,[6] and even left ventricular segmental wall-motion abnormalities.[7]

Among the hepatobiliary disorders that affect patients with diabetes are acalculous cholecystitis and emphysematous cholecystitis. Acalculous cholecystitis is a well-described infectious complication of diabetes mellitus that is being diagnosed with increasing frequency.[8] Emphysematous cholecystitis is usually associated with diabetes.[9] It is also being diagnosed with increasing frequency as a result of the regular use of abdominal ultrasonography in patients with suspected hepatobiliary disease.[10] Since these hepatobiliary infections cause serious morbidity, particularly in elderly patients with diabetes, early diagnosis and aggressive treatment are warranted.[11,12] This patient's clinical course illustrates this important point and once again teaches us that we should include hepatobiliary disease in the differential diagnosis of atypical chest discomfort in patients with diabetes.

REFERENCES

1. Pun KC, Wehner JH. Abdominal pain and massive intravascular hemolysis in a 47-year-old man. Chest 1996;110:1353-5.
2. Hubl W, Mostbeck B, Hartleb H, Pointner H, Kofler K, Bayer PM. Investigation of the pathogenesis of massive hemolysis in a case of *Clostridium perfringens* septicemia. Ann Hematol 1993;67:145-7.
3. Hickman MS, Schwesinger WH, Page CP. Acute cholecystitis in the diabetic: a case-control study of outcome. Arch Surg 1988;123:409-11.
4. Ransohoff DR, Miller GL, Forsythe SB, Hermann RE. Outcome of acute cholecystitis in patients with diabetes mellitus. Ann Intern Med 1987; 106:829-32.
5. Vingan HL, Wohlgemuth SD, Bell JS III. Percutaneous cholecystostomy drainage for the treatment of acute emphysematous cholecystitis. AJR Am J Roentgenol 1990;155:1013-4.
6. Ryan ET, Pak PH, DeSanctis RW. Myocardial infarction mimicked by acute cholecystitis. Ann Intern Med 1992;116:218-20.
7. Patel J, Movahed A, Reeves WC. Electrocardiographic and segmental wall motion abnormalities in pancreatitis mimicking myocardial infarction. Clin Cardiol 1994;17:505-9.
8. Reiss R, Deutsch AA. State of the art in the diagnosis and management of acute cholecystitis. Dig Dis 1993;11:55-64.
9. Wheat LJ. Infection and diabetes mellitus. Diabetes Care 1980;3:187-97.
10. Gill KS, Chapman AH, Weston MJ. The changing face of emphysematous cholecystitis. Br J Radiol 1997;70:986-91.
11. Hickman MS, Schwesinger WH, Page CP. Acute cholecystitis in the diabetic: a case-control study of outcome. Arch Surg 1988;123:409-11.
12. Shpitz B, Sigal A, Kaufman Z, Dinbar A. Acute cholecystitis in diabetic patients. Am Surg 1995;61:964-7.

CORRECTION

Chest Pain with a Surprising Course

Chest Pain with a Surprising Course . On page 1137, in the legend to Figure 2, the magnification for Panel A should have been ×100, and that for Panel B ×1000, not ×10 and ×40, as printed.

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