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Case 3-2006: A 63-Year-Old Woman with Jaundice and a Pancreatic Mass

Robert H. Schapiro, M.D., Michael M. Maher, M.D., and Joseph Misdraji, M.D.

PRESENTATION OF CASE

From the Gastrointestinal Unit (R.H.S.) and the Departments of Radiology (M.M.M.) and Pathology (J.M.), Massachusetts General Hospital; and the Departments of Medicine (R.H.S.), Radiology (M.M.M.) and Pathology (J.M.), Harvard Medical School.

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A 63-year-old woman was admitted to the hospital for evaluation of a pancreatic mass.

Four months before admission, the patient noticed dysuria and dark urine. The results of urinalysis showed 3+ bilirubin and 2+ occult blood and were otherwise normal. A urinary tract infection was diagnosed, and levofloxacin was prescribed. A urine culture subsequently showed no growth of bacteria. Five days after the urinalysis, she went to a local hospital emergency department, where she said that she had had dark urine, pruritus, and intermittent epigastric pain for the preceding 10 days; a weight loss of 5 kg during the past 3 months; and lightening of the color of her stool and a small purple area on her right arm for the past several days. The patient had not had fever, chills, nausea, vomiting, or diarrhea. Abdominal computed tomography (CT) revealed dilatation of the intrahepatic and extrahepatic ducts and enlargement of the pancreatic head. She was transferred to this hospital and admitted.

The vital signs were normal. On examination, the patient appeared well and was alert and oriented but jaundiced. The sclerae were icteric, and there was an ecchymosis (2 cm in diameter) on her right thigh; the remainder of the physical examination was normal. The levels of electrolytes, calcium, phosphorus, magnesium, and serum lipids; the results of renal-function studies; and the white-cell, differential, and platelet counts were normal. The results of other laboratory tests are shown in Table 1. A chest radiograph showed two small ill-defined opacities at both lung apexes. Abdominal and pelvic CT scanning on the second hospital day, performed after the administration of oral and intravenous contrast material, revealed dilated intrahepatic and extrahepatic bile ducts; a periportal lymph node that was 7 mm in diameter; a periportal mass, 3.1 cm by 3.6 cm; a complex cystic mass, 2.9 cm by 2.4 cm, in the pancreatic head; another complex cystic mass, 2.7 cm by 1.4 cm, adjacent to the pancreatic tail; and a low-density splenic lesion.

Abdominal ultrasonography on the next day confirmed the presence of dilated intrahepatic and extrahepatic bile ducts and a complex cystic mass in the pancreatic head. She had a normal gallbladder. Endoscopic upper-abdominal ultrasonography revealed no abnormalities in the esophagus, stomach, or duodenum. There was a round, thick-walled cystic mass in the pancreatic head, 2.9 cm by 2.4 cm, that abutted

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Table 1. Laboratory Test Results.*

Variable	1st Admission	2nd Hospital Day	3rd Hospital Day	4th Hospital Day	10th Hospital Day	6 Weeks before 2nd Admission	2nd Admission
Hematocrit (%)	30.5						25.9
Hemoglobin (g/dl)	9.7						8.1
White-cell count (per mm^3)	5,600						7,500
Platelet count (per mm^3)	292,000						241,000
Mean corpuscular volume (μm^3)	71						70
Bilirubin (mg/dl)							
Conjugated	3.2	3.0		2.8	0.9	0.4	0.2
Total	6.0	5.2		5.1	1.4		0.6
Protein (g/dl)							
Total	8.5	7.3		6.9	7.2	7.7	8.3
Albumin	3.2	2.7		2.5	2.7	3.2	
Globulin	5.3	4.6		4.4	4.5	4.5	
Iron (μg/dl)		64					
Iron-binding capacity (μg/dl)		276					
Ferritin (ng/ml)		100	105				
Alkaline phosphatase (U/liter)	655	563		538	348	100	172
Aspartate aminotransferase (U/liter)	219	229		241	105	18	
Alanine aminotransferase (U/liter)	196	184		208	123	13	
Lactate dehydrogenase (U/liter)	216						155
Amylase (U/liter)	26	18		294	34		28
Lipase (U/dl)	3.8	2.4		119.9	6.6		
Carcinoembryonic antigen (ng/ml)		0.9					
Alpha-fetoprotein (ng/ml)		6.7	7.1				
CA 19-9 (U/ml)		1	1				

* To convert the values for conjugated and total bilirubin to micromoles per liter, multiply by 17.1. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.

and possibly invaded the superior mesenteric vein. A fine-needle aspiration biopsy of the mass was performed; cytologic examination showed rare reactive epithelial cells, acute and chronic inflammation, and no malignant cells. Endoscopic retrograde cholangiopancreatography (ERCP) with contrast medium revealed a diffusely dilated biliary tree above a localized 10-mm-long stenosis of the middle third of the common bile duct. A sphincterotomy was performed, and afterward a stent was placed in the common bile duct; flow of bile was seen through the stent. The patient's temperature rose to 37.9°C in the 24 hours after the procedure and then returned to normal. The results of laboratory tests are shown in Table 1.

On the 10th hospital day, laparoscopic examination showed no evidence of metastatic carcinoma. Cytologic examination of peritoneal washings revealed mesothelial and inflammatory cells. The results of laboratory tests are shown in Table 1. The patient was discharged to her home, with instructions to take cholestyramine (4 g, twice daily), hydroxyzine (25 mg, four times daily), and oxycodone and acetaminophen (as needed for pain).

Three weeks later, a CT-guided core biopsy of the pancreas performed in the outpatient department revealed necrotizing granulomatous inflammation in soft tissue; no pancreatic tissue was identified. Cytologic examination showed rare atypical epithelial cells, acute inflammation, multinucleated giant cells, and epithelioid histiocytes forming vague granulomas.

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One month later (approximately six weeks before the current admission), repeated abdominal and pelvic CT scanning with contrast medium showed the stent in place with decreased bile-duct dilatation and a soft-tissue mass in the porta hepatis that was slightly decreased in size. The complex cystic mass in the head of the pancreas had decreased in size. The periportal lymphadenopathy, the cystic mass adjacent to the pancreatic tail, and the splenic lesion were unchanged. There were enlarged retroperitoneal lymph nodes, the largest of which was 1.5 cm by 1.6 cm. The nodes had low-density centers with enhancing rims. Chest radiography showed two small, ill-defined bilateral apical opacities; there were no abnormalities visible in the lungs, the mediastinum, or the heart.

Two weeks before the patient's admission, outpatient endoscopic ultrasonography and ERCP were repeated. The ERCP showed a persistent stricture of the middle third of the main bile duct and a patent sphincterotomy. The stent was changed, and cytologic analysis of bile-duct brushings was negative for malignant cells. Endoscopic ultrasonography showed an unchanged mass in the porta hepatis, a decrease in the size of the pancreatic-head mass, and extensive intraabdominal lymphadenopathy. Cytologic analysis of a fine-needle aspirate of the porta-hepatis mass and a perigastric lymph node showed a few glandular cells and features of a reactive lymph node, respectively. No malignant cells were identified in either specimen. Special stains for acid-fast bacilli were negative, and flow-cytometric analysis for hematopoietic cell-surface markers revealed no abnormal cells. The patient was admitted to the hospital.

The patient had noted nasal congestion, with white discharge, and a nocturnal cough with watery sputum for the past year, without fever or chills. The color of her stool had returned to normal after the medical interventions four months earlier. She had no allergies or exposure to toxins, and she did not drink alcohol, smoke, or use illicit drugs. She had immigrated to the United States from the Dominican Republic one year earlier and lived with her family. Her mother and three brothers had died of cerebrovascular disease, a sister of a myocardial infarction at 53 years of age, another brother of liver cancer, and her father of asthma.

The vital signs and physical examination were normal. A chest radiograph revealed stable bilateral apical lung opacities. The results of urinalysis, white-cell, differential, and platelet counts, electrolyte measurements, and renal-function tests were normal. Other laboratory-test results are shown in Table 1.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Robert H. Schapiro: May we review the radiologic studies?

Dr. Michael M. Maher: A contrast-enhanced CT scan of the abdomen obtained during the patient's first admission shows intrahepatic and extrahepatic biliary dilatation and a small, low-density lesion in the spleen (Fig. 1A). There is a mass that is 3.2 cm in diameter at the porta hepatis, which is of soft-tissue density (Fig. 1B). In the region of the pancreatic tail, there is an extrinsic soft-tissue abnormality, with a low-density center and an enhancing rim (Fig. 1C). The extrahepatic biliary dilatation extends to the level of the pancreatic head, where there is a cystic lesion (Fig. 1D); the wall of this lesion was enhanced after the intravenous administration of contrast material, suggesting that this is a complex cystic lesion.

An ultrasonographic study confirmed the presence of intrahepatic and extrahepatic biliary dilatation. The pancreatic mass is clearly visible (Fig. 1A of the Supplementary Appendix, available with the full text of this article at www.nejm.org); ultrasonography shows the internal architecture of this mass, with septations and a thick wall (Fig. 1B of the Supplementary Appendix), confirming its complexity. An ERCP confirmed the presence of intrahepatic and extrahepatic biliary dilatation to the level of the common bile duct, where there was a stricture (Fig. 2), which was stented.

A second abdominal CT scan obtained approximately two months after the first one shows that there is no residual intrahepatic biliary dilatation, suggesting successful decompression with the stent. The cystic mass in the head of the pancreas is almost fully resolved (Fig. 1E). Multiple enlarged retroperitoneal lymph nodes have developed in both the right and left periaortic regions. These lesions, like many of the others, have low-density centers with enhancing rims.

Dr. Brenna C. Bounds (Gastroenterology): A second endoscopic ultrasonographic evaluation and

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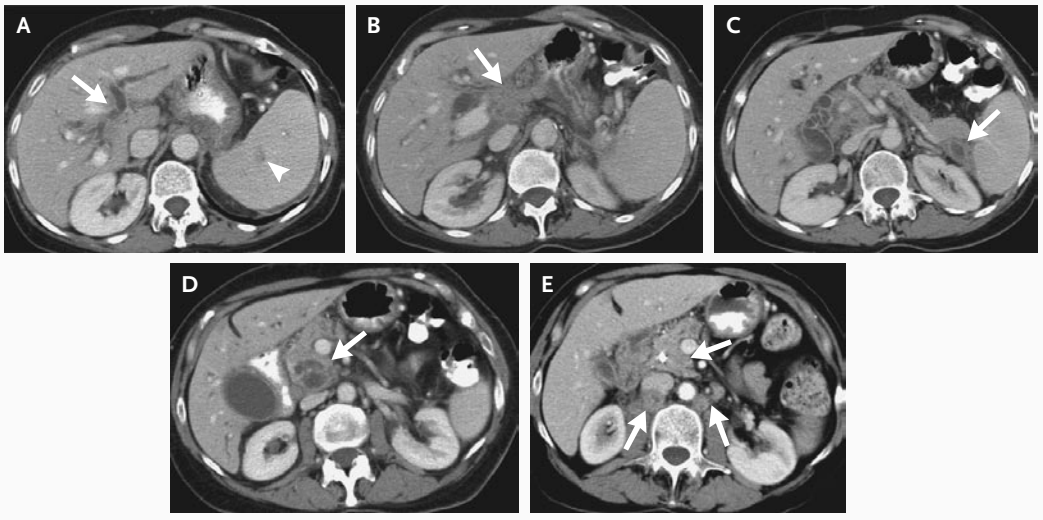


Figure 1. Contrast-Enhanced CT Images of the Abdomen.

There is intrahepatic biliary dilatation (Panel A, arrow). In the spleen, there is a low-density lesion, less than a centimeter in diameter (Panel A, arrowhead). There is a mass, 3.2 cm in diameter, at the porta hepatis (Panel B), which is of soft-tissue density (arrow). A soft-tissue abnormality (Panel C), with a low-density center and an enhancing rim, is seen extrinsic to the pancreatic tail (arrow). There is a cystic lesion in the pancreatic head (Panel D, arrow). Repeated contrast-enhanced CT scanning performed two months after the first scanning (Panel E) shows that the cystic mass in the head of the pancreas is almost fully resolved. Since the earlier CT scan was obtained, multiple enlarged retroperitoneal lymph nodes with central hypodensity and enhancing rims have developed (arrows) in the right and left periaortic regions.

an ERCP were performed two weeks before the patient's most recent admission. The ERCP confirmed the disappearance of the mass in the head of the pancreas. Endoscopic ultrasonography showed a normal pancreatic head. Between the head of the pancreas and the porta hepatis, there was a mass with several cystic areas, suggesting areas of necrosis. Multiple lymph nodes were seen in the porta hepatis and in the perigastric area, the gastrohepatic ligament, and the periaortic area. A needle was passed out of the echoendoscope into a lymph node to take samples for cytologic analysis.

Dr. Schapiro: This 63-year-old woman, a recent immigrant from the Dominican Republic, presented with biliary obstruction apparently related to a cystic mass in the head of the pancreas. Confounding factors included a second cystic mass near the tail of the pancreas, other masses in the porta hepatis and spleen, and progressive abdominal lymphadenopathy. Cancer was suspected, but biopsy specimens showed only granulomatous changes. The patient was followed for four months, during which her disease followed an indolent course. Finally, a diagnostic procedure was performed.

Clearly, this patient's jaundice was due to extrahepatic biliary obstruction. The causes of extrahepatic bile-duct obstruction include primary tumors of the head of the pancreas, cystic neoplasms such as intraductal papillary mucinous neoplasms, and tumors of the bile ducts. Metastatic tumors to the porta hepatis originate most commonly in the colon, breast, and lung, but they may also be from the ovary, kidney, and other organs. Lymphomas in porta-hepatis nodes may compress the duct or involve it directly. Inflammatory processes include chronic or autoimmune pancreatitis, sclerosing cholangitis, human immunodeficiency virus (HIV) cholangiopathy, and various chronic infections, such as *Mycobacterium avium* complex or *M. tuberculosis*. Intraluminal obstruction of the bile duct can result from stones, parasites, and polyps. Since no intraluminal problems were seen on ERCP, and in view of the clear extrabiliary manifestations of disease, I will exclude this last category from consideration.

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Figure 2. Endoscopic Retrograde Cholangiopancreatogram Obtained at the First Admission.
There is a smooth stricture of the middle third of the common bile duct (arrow).

NEOPLASTIC CAUSES OF BILE-DUCT OBSTRUCTION

The treating physicians in this case apparently suspected cancer and made a variety of efforts to confirm its presence, all of which were negative. How reliable are these negative results in ruling out cancer? A review of biliary-brush cytology reported a sensitivity ranging from 37 percent to 68 percent for the detection of cancer cells in malignant obstruction, with a specificity of 100 percent.[1] Better results occur if tissue is obtained by biopsy, but a negative cytologic result certainly does not rule out cancer. Cytology is useful in diagnosing cancer or even the mucinous nature of a pancreatic cyst in only 50 percent of cases.[2,3] Core-biopsy samples of the pancreas may be more reliable, but the best estimates give a sensitivity of 70 to 80 percent.

We might have had a better idea as to the nature of the biliary obstruction if a pancreatogram had been obtained at the time of ERCP. Wire-guided cannulation of the bile duct before the injection of contrast material reduces the risk of post–ERCP pancreatitis. Unfortunately, once a sphincterotomy has been performed, the ability to view the pancreatic duct during that ERCP is markedly decreased.

Let us turn to the complex cystic masses in the head and near the tail of the pancreas. Cystic lesions may represent benign serous cystadenomas, premalignant or malignant mucinous cystadenomas, intraductal papillary mucinous tumors, inflammatory pseudocysts,[3] or rarely, cystic islet-cell tumors. All of these lesions may present with pancreatobiliary obstruction. The progressive lymph-node changes seen on the second admission and the porta-hepatis mass suggest that if these cystic lesions are neoplastic, they are malignant. Tumor markers, including carcinoembryonic antigen, alpha-fetoprotein, and CA 19-9, if measured in cyst fluid, can be useful in the differential diagnosis of cystic lesions of the pancreas,[4] but such studies were not done in this case.[3] Nonetheless, the presence of any malignant tumor seemed unlikely by the time of the current admission, since some of the lesions had clearly improved in the absence of therapy, even as new ones had developed. In view of this indolent and paradoxical course, we should turn our attention to nonmalignant entities.

NON-NEOPLASTIC CAUSES OF BILIARY OBSTRUCTION

Chronic pancreatitis can produce secondary biliary obstruction. This patient has none of the usual risk factors for chronic pancreatitis. Autoimmune pancreatitis, first described in 1961 but generally recognized only in the past 10 years,[5] is associated with usually diffuse but occasionally focal enlargement of the pancreas and diffuse or segmental irregular narrowing of the main pancreatic duct, mimicking cancer.[6] Hyperglobulinemia and autoimmune markers and a characteristic lymphoplasmacytic infiltrate with fibrosis on pancreatic biopsy are frequently present, and there is often a striking response to corticosteroid therapy. Peripancreatic lymph-node enlargement is common, as are sclerosing cholangitis-like changes in the bile duct. The levels of pancreatic enzymes are usually normal or only slightly elevated. Although many features of autoimmune pancreatitis were present in this case and the course suggests a nonmalignant process, I cannot really warm to this diagnosis for several reasons. Cystic changes in the pancreas are improbable in this condition, the pancreatic enlargement

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in this patient was quite focal, whereas the progressive lymphadenopathy seems to have been more diffuse in the abdomen, and most important, the findings on biopsy were very different from the lymphoplasmacytic changes that would be expected with autoimmune pancreatitis.

Two of the most striking features of this case were the demonstration of granulomas on a CT-guided core biopsy of the pancreas and the multinucleated giant cells seen on cytologic examination. Granulomas are a feature of a variety of infectious and inflammatory diseases.[7] Infections that fall in this category include those caused by mycobacteria, other bacteria such as brucella and syphilis, fungi, parasites such as leishmania and toxoplasmosis, viruses such as cytomegalovirus (CMV), and even rickettsia, such as Q fever. Other granulomatous conditions include sarcoidosis, lymphomas, Wegener's granulomatosis, Crohn's disease, Whipple's disease, and drug reactions.

Of the entities I just mentioned, most have rarely, if ever, been associated with biliary obstruction.[8] The only relevant entities are tuberculosis, lymphomas, and sarcoidosis. CMV and cryptococcal infections are thought to be involved in HIV cholangiopathy but should not cause the extensive extrabiliary manifestations seen in this patient. Sarcoidosis is a very rare cause of biliary obstruction, and the case reports I could find all involved the intrahepatic ducts.[9] In the absence of characteristic pulmonary involvement, I think we can rule out sarcoidosis.

Both Hodgkin's lymphoma and non-Hodgkin's lymphomas can be associated with granulomas, obstruct the bile duct, and lead to progressive lymphadenopathy.[10-12] Marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue can be especially indolent. Are the findings here compatible with lymphoma? I think not. Cystic changes such as those present in the head of the pancreas would be highly unusual in lymphoma. In addition, flow-cytometric analysis of a lymph-node aspirate showed no evidence of a monoclonal B-cell population. Lymph nodes with hypodense centers on imaging are more typical of infection than of lymphoma. Finally, although lymphomas may be indolent, they should not spontaneously regress.

In contrast, tuberculosis seems a likely culprit in this case. Numerous examples of tuberculous biliary obstruction are present in the literature,[13-16] going all the way back to a Case Records discussion at this hospital in 1951.[17] Tuberculosis may cause biliary obstruction either by compression of the bile duct by tuberculous lymphadenitis or, occasionally, by direct infection of the duct itself, with acid-fast organisms detected on biliary cytology.

How does this case stand up as a possible example of intraabdominal tuberculosis? The patient was a recent immigrant from a nation where public health and sanitary standards are less rigorous than in the United States. The absence of fever is more compatible with tuberculosis than with a more acute infection. The presence of multiple areas of abdominal involvement, some of which improved whereas others progressed over four months, could occur in mycobacterial infection. Although acid-fast staining on the biopsy specimen was negative, human tubercle bacilli are characteristically difficult to identify by staining.

M. avium complex may cause changes similar to those of tuberculosis in a severely immunocompromised patient. We have no reason to think that this patient was infected with HIV. Acid-fast organisms are easier to demonstrate in *M. avium* complex infection than in tuberculosis. On CT scanning, lymphadenopathy is usually of a more homogeneous, dense nature. In summary, the granulomas in the pathological specimens, the CT appearance, and the prolonged course are all factors that strongly suggest that this patient had an intraabdominal infection with *M. tuberculosis*. The diagnostic procedure was presumably an excisional lymph-node biopsy.

Dr. Nancy Lee Harris (Pathology): Dr. Bounds, would you summarize the clinical thinking?

Dr. Bounds: Although the initial suspicion was that the patient had a pancreatic carcinoma, the resolution of the pancreatic mass, in the absence of specific therapy for cancer, suggested infection, including tuberculosis. We also considered the possibility of lymphoma. When the second fine-needle aspiration biopsy and flow cytometry showed no evidence of carcinoma, lymphoma, or acid-fast bacilli, the patient was readmitted for a Roux-en-Y choledochojejunostomy, for definitive treatment of her bile-duct stricture, and an excisional biopsy of several enlarged lymph nodes.

CLINICAL DIAGNOSIS

Probable intraabdominal tuberculosis.

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DR. ROBERT H. SCHAPIRO'S DIAGNOSIS

Intraabdominal infection with *Mycobacterium tuberculosis,* with secondary biliary obstruction.

PATHOLOGICAL DISCUSSION

Dr. Joseph Misdraji: The initial fine-needle aspiration cytology specimen showed abundant acute inflammation, consistent with the contents of an abscess. The fine-needle aspirate obtained at biopsy one month later showed a similar background, but with a few multinucleated histiocytic giant cells and with clusters of epithelioid histiocytes forming vague granulomas (Fig. 3A). The accompanying core-biopsy specimens revealed fibrotic tissue with scattered granulomas, some with central necrosis. No pancreatic tissue was seen. Staining for acid-fast bacilli and fungi was negative.

The diagnostic procedure was excisional biopsy of paraduodenal and periportal lymph nodes, which showed a necrotizing granulomatous lymphadenitis (Fig. 3B). Staining for acid-fast bacilli and fungi was again negative. However, cultures of these lymph nodes yielded growth of *M. tuberculosis.*

Pancreatic tuberculosis usually occurs in the setting of miliary tuberculosis, although even then, it occurs in only 2 to 5 percent of cases.[18,19] The incidence of pancreatic tuberculosis has increased recently, presumably because of the increase in travel to and from countries where tuberculosis is common, the HIV pandemic, and the worldwide resurgence of *M. tuberculosis.*[20] It is seen in three main settings[21]: in patients from developing countries where tuberculosis is endemic[20,22,23]; in patients who are infected with HIV or otherwise immunocompromised[24]; and in cases that occur sporadically.[20,25,26] Tuberculosis can affect the pancreas either by contiguous spread from peripancreatic lymph nodes or by way of hematogenous spread from an occult focus in the lung.[20,27] The manifestation of the disease is usually that of a pancreatic mass mimicking carcinoma,[27-31] but it can also occur as obstructive jaundice, a pancreatic abscess, and acute or chronic pancreatitis.[8,32-37] Often, there are no signs of tuberculosis elsewhere.[24,25,29] Pancreatic tuberculosis should be considered in the differential diagnosis of pancreatic masses in patients who have lived in or traveled to areas in which tuberculosis is endemic, in those with a history of exposure to tuberculosis, in young patients, in patients with clinical signs of infection such as fever, and in HIV-infected patients.[20,29]

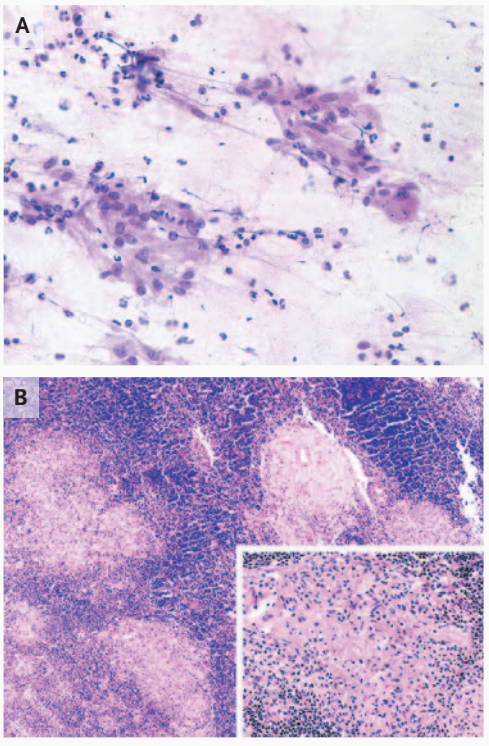


Figure 3. Biopsy Specimens.
In the fine-needle aspiration biopsy smears (Panel A), clusters of epithelioid histiocytes forming vague granulomas were present. Scattered neutrophils are present in the background (Papanicolaou stain). Examination of paraduodenal lymph nodes excised during the biliary bypass procedure (Panel B) shows granulomatous lymphadenitis. A high-power view (inset) shows the presence of caseating necrosis within the granuloma (hematoxylin and eosin stain). No acid-fast bacilli were observed on special staining.

The diagnosis of pancreatic tuberculosis usually requires pathological examination of tissue from the pancreas or peripancreatic lymph nodes. Fine-needle aspiration biopsy has a reported sensitivity for pancreatic tuberculosis of about 50 percent for percutaneously obtained specimens.[20,24,26,30] Acid-fast staining of pathological material demonstrates organisms in only about 20 to 40 percent of cases, and culture is about 77 percent sensitive.[20] Polymerase-chain-reaction assays have proved useful in identifying mycobacteria in pathological material, although the

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results offer no information regarding drug susceptibility and therefore are best used as an adjunct to standard culture.[20]

Dr. Harris: Dr. Daskalakis, can you discuss the management and follow-up of this patient?

Dr. Demetre Daskalakis (Infectious Diseases): Because of the patient's country of origin, we had a very low index of suspicion for multidrug-resistant tuberculosis, so we initiated a four-drug regimen with isoniazid, rifampin, ethambutol, and pyrazinamide with pyridoxine. One month later, the organism was reported to be fully susceptible, and ethambutol and pyrazinamide with pyridoxine were discontinued. On reevaluation at two months after treatment, the patient was feeling well, her appetite had returned, and she had gained about 2.3 kg. Over the course of the next nine months, imaging studies showed resolution of the lymphadenopathy and the cystic peripancreatic lesion, although the splenic lesion persisted. Because lymphadenitis can recur even after 9 months of therapy, we planned to treat her for 12 months with isoniazid and rifampin. Eleven months into her course, abnormalities on liver-function tests developed, and we discontinued these therapies. At last report, she was completely well.

ANATOMICAL DIAGNOSIS

Mycobacterium tuberculosis infection of the pancreas and peripancreatic lymph nodes.

No potential conflict of interest relevant to this article was reported.

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