EDUCATION PRACTICE

A 50-Year-Old Woman With Unexplained Recurrent Pancreatitis

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Clinical Scenario

A 50-year-old woman presents to your emergency department with her second attack of acute pancreatitis. Two months ago she developed severe epigastric pain radiating to the back, associated with nausea and vomiting. She was evaluated and admitted at that time. On admission, she had a lipase of 1725 U/L, AST 45 U/L, ALT 50 U/L, normal alkaline phosphatase and bilirubin, calcium 8.6 mg/dL, albumin 3.8 g/dL, triglycerides 320 mg/dL, and a white blood cell count of 11,000/mm^3. She was hospitalized for 5 days, during which time you saw her in consultation.

Her medical history was notable for diabetes mellitus for the last 5 years, hypertension, hyperlipidemia, adenomatous colonic polyps, and degenerative joint disease. Her medications included lisinopril, furosemide, simvastatin, metformin, metoprolol, aspirin, Premarin, and occasional senna. In addition, she had received trimethoprim-sulfamethoxazole for a urinary tract infection for the 5 days previous to the attack of acute pancreatitis. She smoked ½ pack daily and used alcohol "only on special occasions." Her family history was negative for pancreatitis or pancreatic malignancy.

You recommended an abdominal ultrasound, which demonstrated a normal gallbladder without stones or sludge, the common bile duct was 5 mm, and the liver appeared fatty. The pancreas was not visualized as a result of overlying bowel gas. An abdominal computed tomography (CT) scan with pancreas protocol was performed 2 days into her hospitalization, which revealed mild diffuse pancreatic enlargement with peripancreatic edema and stranding but no necrosis or fluid collections. There was also no pancreatic mass, ductal dilation, or calcification. Her pancreatitis was attributed to the trimethoprim-sulfamethoxazole, which she was counseled to avoid in the future. She recovered and was discharged on a low fat diet.

Two months after discharge she develops a similar attack and returns to the emergency department, at which time you are called to evaluate her. She reports she is avoiding alcohol but continues to smoke. She reports no new medications and is following a very low fat diet. Her physical exam now reveals a moderately overweight woman in marked distress as a result of pain and vomiting. Her vital signs include a temperature of 37.5°C, pulse of 102, blood pressure 154/79 mm Hg, respiratory rate of 18, and body mass index of 36. Her physical examination is significant for abdominal tenderness in the mid-epigastrium, with focal involuntary guarding and hypoactive bowel sounds but no rebound. Laboratory tests at this time include lipase 1400 U/L, AST 41 U/L, ALT 46 U/L, normal alkaline phosphatase and bilirubin, calcium 8.9 mg/dL, triglycerides 270 mg/dL, albumin 3.9, and total protein 7.8. You order a repeat abdominal ultrasound, which again shows a normal gallbladder and bile duct and fatty liver. She is made nothing by mouth and treated with intravenous fluids, analgesics, and anitiemetics. Within 48 hours, she is substantially improved.

The Problem

Central to the management of acute pancreatitis, and especially acute relapsing pancreatitis, is identifying the cause. Knowing the cause allows the best chance of intervening to prevent subsequent attacks. Preventing subsequent attacks is the key to preventing the development of a chronic inflammatory milieu within the pancreas, the activation of pancreatic stellate cells, and the progression toward chronic pancreatitis. In the United States and all other developed countries, the most common causes of recurrent acute pancreatitis are gallstones and alcohol. Together, these account for at least three fourths of all cases. This patient, who does not obviously drink alcohol and does not have gallstones on 2 abdominal ultrasound examinations, presents a case of unexplained pancreatitis. Before labeling this as idiopathic, there are a number of potential etiologies that need to be excluded. First, can we truly exclude alcohol and gallstones? Because there is no laboratory test to accurately exclude alcohol as the cause, we rely on history (from the patient or the family). Many astute clinicians have been fooled in this regard, finding out later from a family member that the patient drinks heavily. Likewise, it can be difficult to completely exclude gallstones if one considers both macrolithiasis (visible on ultrasound) and microlithiasis. Almost by definition, microlithiasis implies the condition is not (easily) visible to conventional imaging studies. In reality, many of the studies evaluating patients with unexplained or idiopathic pancreatitis, later diagnosed to be due to microlithiasis, included patients with gallbladder sludge present on the initial ultrasound. This patient has no visible sludge or stones on 2 separate ultrasound examinations, but she does have minor elevations in liver chemistries that could be consistent with microlithiasis. Because stones or sludge might be seen on subsequent ultrasound examinations even if the first is negative, a repeat ultrasound is very reasonable in this situation.

Abbreviations used in this paper: ANA, antinuclear antibody; CFTR, cystic fibrosis transmembrane conductance regulator; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MR, magnetic resonance; SPINK-1, serine protease inhibitor kazal type 1.

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In those who do not have obvious gallstones and in those who do not drink alcohol in sufficient quantities to cause pancreatitis, a number of other etiologies need to be considered. In this patient, drug-induced pancreatitis was initially considered. Although many drugs can cause pancreatitis, very few do it with any regularity. The most commonly offending drugs are 6-mercaptopurine and azathioprine, but many others have been implicated less commonly and include 4 of relevance to this patient: estrogens, sulfa drugs, statins, and furosemide. Although drug-induced pancreatitis was an appropriate consideration at the first attack, it seems somewhat less likely with the recurrence while off the initially identified potential offending drug, although the patient remains on other drugs that could be implicated.

Next on the list of potential etiologies would be conditions that cause pancreatitis by blocking the pancreatic duct. These could include ampullary or pancreatic malignancy (including intraductal papillary mucinous neoplasms), benign pancreatic duct strictures (eg, induced by the initial attack of pancreatitis), ampullary strictures (from previous passage of stones or duodenal disease affecting the ampulla such as Crohn's disease or celiac disease), duodenal diverticula, pancreas divisum, pancreatic sphincter of Oddi dysfunction, and others. None of these entities can be ruled out on the basis of the evaluation so far. Benign and malignant strictures seem less likely, given the absence of a dilated pancreatic duct on the previous CT scan, but a multi-slice pancreas protocol CT now might disclose such a finding. Obviously, missing an underlying malignancy would be a serious diagnostic error.

Hyperlipidemia and hypercalcemia might both be associated with acute pancreatitis. In this patient, modest hypertriglyceridemia has been documented but not to the level that can cause acute pancreatitis. This patient is also on a drug that can raise triglyceride levels (estrogens). Some patients wait a period of time before being evaluated, and because they are usually nothing by mouth during this time, the initial triglyceride level obtained might be falsely low. Repeating the triglyceride measurement after recovery (and even after a fatty meal) might disclose a more substantial elevation.

A variety of genetic mutations have been described in association with pancreatitis, but primarily with chronic rather than acute pancreatitis. In this patient, although the current clinical situation is most consistent with acute pancreatitis, many of these patients with acute relapsing disease will eventually develop chronic pancreatitis and more chronic symptoms. We should not exclude the possibility of a genetic contribution in this patient, although we might wish to wait until there is more clear evidence of chronic pancreatitis before we consider evaluating for the known mutations associated with pancreatitis. These mutations occur in the trypsinogen (*PRSS-1*) gene, serine protease inhibitor kazal type 1 (*SPINK-1*) gene, and cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Mutations in the trypsinogen gene usually produce an autosomal dominant pattern of inheritance, which is not present in this patient's family history. Mutations in *CFTR* or *SPINK-1* are possible. Unlike mutations in *SPINK-1*, which are looked on more as co-factors that might combine with environmental factors to produce pancreatitis, certain types of *CFTR* mutations may be enough, in and of themselves, to cause pancreatitis.

Autoimmune pancreatitis is being increasingly recognized. Most commonly, it presents as unexplained chronic pancreatitis or mimics pancreatic carcinoma. It might, however, present initially with acute or acute relapsing pancreatitis, often with a bulky or diffusely enlarged pancreas on imaging studies. Autoimmune pancreatitis is most often associated with increased levels of IgG subclass 4, although this elevation is seen more commonly in patients from Asia as compared with those from the U.S. Autoimmune pancreatitis is actually a multi-system disease, because IgG4-bearing plasma cells can be seen infiltrating not only the pancreas but also the salivary glands, retroperitoneum, bile ducts, ampulla, and other organs. These patients might have associated autoimmune diseases like scleroderma, Sjogren's disease, thyroiditis, and others and might have elevations in antinuclear antibody (ANA) as well. This condition is also a possibility in this patient.

Other potential causes of acute pancreatitis such as pancreatic trauma, insecticide poisoning, scorpion bites, thromboembolic disease, severe hypotension, and others are highly unlikely in this patient.

Management Strategies and Supporting Evidence

The management strategy for this patient might need to incorporate both diagnostic and therapeutic maneuvers. The basic initial evaluation for acute pancreatitis includes a careful history and physical examination, laboratory tests (amylase or lipase, liver chemistries, calcium, and triglycerides), and an imaging study (ultrasound and/or CT scan). This initial work-up serves to identify those with the most common etiologies. In many patients with a negative initial work-up, they might only experience a single attack of pancreatitis (less than 10% appear to develop recurrent attacks). This would suggest that a course of observation would be most appropriate for those with a single attack, with a more involved evaluation reserved for those with multiple attacks (or perhaps one severe attack). On the other hand, underlying malignancy might be seen in a small subset of these patients, which would suggest that we should evaluate patients after even a single attack to detect the small percentage of patients with underlying malignancy (likely less than 5% overall). These considerations have translated into an approach to evaluate those most at risk of malignancy (older patients, beyond 40 or 45) after even a single mild attack. The recommended evaluation in these patients to rule out malignancy could include a high-quality CT scan or endoscopic ultrasonography (EUS). In those with multiple attacks, like this patient, a more extensive evaluation is recommended.

In this patient, we must consider the following potential etiologies. Pancreatic duct obstruction of any cause remains on the differential, including malignant disease, but also diseases like pancreas divisum and sphincter of Oddi dysfunction remain. These latter 2 are controversial, and disagreement exists from center to center and clinician to clinician as to their importance. Hyperlipidemia and drug-induced pancreatitis are possible, although less likely. Genetic mutations are also possible, as is autoimmune pancreatitis. In most large case-series of patients with unexplained acute pancreatitis, microlithiasis is actually the most common diagnosis, and this also must be considered in this patient.

Given that we need to rule out malignancy (the most concerning cause) and microlithiasis (in some studies the most common cause) early in the diagnostic process, the initial focus should be on these. Although microlithiasis is defined by microscopic stones and crystals in the bile, there are no standardized method for analyzing bile and no uniformly accepted definition of what microscopic findings are sufficient to diagnose microlithiasis. In fact, there is some evidence that EUS is at least equivalent and probably superior to microscopic bile analysis. Performing an EUS would also be a very reasonable way to assess for possible underlying pancreatic and ampullary malignancy and allow a visual inspection of the ampulla. If EUS is not available, an alternative would be a high-resolution, multi-slice pancreas protocol CT scan. Alternatively, although current resolution is not as good as a CT scan, magnetic resonance (MR) imaging with MR cholangiopancreatography could be performed. If there is a question as to whether this patient might have hyperlipidemic pancreatitis, one could measure fasting (or even postprandial) triglyceride levels after recovery. Finally, one could measure ANA and IgG4 to look for autoimmune pancreatitis.

If this type of more extensive evaluation (eg, EUS and the serum tests identified above) is unremarkable, then the options are (1) follow the patient conservatively; (2) consider genetic testing; (3) empiric cholecystectomy; or (4) consider endoscopic retrograde cholangiopancreatography (ERCP), with a plan to perform sphincter of Oddi manometry at that time. There is no evidence base that tells us which approach is best. Genetic testing in this setting might be misleading; if 1 or 2 minor *CFTR* mutations are identified, does that mean that these explain the pancreatitis? The answer to this question is often no. Given that microlithiasis is the most common diagnosis in some studies and that bile analysis (and to a lesser degree EUS) might miss microlithiasis, some would advocate for an empiric cholecystectomy before considering ERCP. Others would recommend therapy with ursodeoxycholic acid as an alternative, although the dose and duration are unknown. This approach of empiric cholecystectomy is not unreasonable in patients with more than 1 attack of acute pancreatitis. Certainly, if the EUS demonstrates gallbladder sludge or evidence of microlithiasis (or if bile analysis is used and demonstrates the same), then cholecystectomy is recommended before any further study. If the EUS is truly normal and of high quality, however, one could consider proceeding to ERCP. It would also be reasonable to consider MR cholangiopancreatography if it has not been done, because this might identify pancreas divisum. If ERCP is undertaken, it should be with the capability of both sphincter of Oddi manometry and minor papilla therapy, if it is required. ERCP should also only be undertaken if there is the technical skill to place small pancreatic duct stents to reduce the risk of post-ERPC pancreatitis.

Areas of Uncertainty

There are multiple areas of uncertainty in the approach identified above. First, because several variations of approaches were recommended, it is obvious that no single strategy is always preferred. The importance of microlithiasis as a frequent cause of pancreatitis is based on old studies with relatively poor quality imaging, and it is likely that modern ultrasound imaging misses far fewer patients with microlithiasis. Microlithiasis itself, on the basis of a definition with nonstandardized techniques of microscopic bile analysis, is a nebulous concept. The role and efficacy of empiric cholecystectomy, a strategy that is based on these older studies, are also not clear. The role of genetic testing continues to evolve, and the interpretation of currently available genetic testing is often not clear. The finding of a genetic mutation does not currently translate into any specific therapeutic approaches. The sensitivity and specificity of ANA and IgG4 in autoimmune pancreatitis (particularly in Western populations) are not known. There remain substantial controversy and disagreement as to whether pancreas divisum and sphincter of Oddi dysfunction are causes of pancreatitis. If ERCP is pursued and one of these diagnoses is found, the efficacy of endoscopic therapy is not well-defined.

Published Guidelines

The AGA Institute Practice Guidelines recommend an initial evaluation for etiology that should include a careful history and physical examination, laboratory testing (to include at a minimum amylase or lipase, liver chemistries, triglycerides, and calcium), and high-quality imaging (both a US and CT scan). In this patient, the initial identification of possible drug-induced pancreatitis was appropriate, but the AGA guidelines would recommend an EUS in this patient after even a single attack to look for underlying malignancy, if the diagnosis of drug-induced disease was not entirely clear. At the second attack, the guidelines recommend repeating the initial evaluation but also recommend proceeding with EUS (or a high-quality CT or MR imaging/MR cholangiopancreatography). The guidelines do allow empiric cholecystectomy as a therapeutic alternative if this initial evaluation is unrevealing, but they do not recommend this approach. ERCP is only recommended after this investigation fails to reveal a cause (or relapses occur after cholecystectomy), and the guidelines recommend that the procedure be done by someone with sufficient technical skill and experience to perform sphincter of Oddi manometry, minor papilla therapy, and place pancreatic duct stents.

Recommendations for This Patient

In this patient, we would measure a repeat fasting triglyceride level (and a postprandial level if the fasting level was of an indeterminate level between 500 and 1000 mg/dL), ANA, and IgG4. We would proceed with EUS, and if gallbladder sludge or other evidence of microlithiasis was identified, we would recommend cholecystectomy. If EUS identified underlying malignancy, we would initiate appropriate medical or surgical management. If the EUS was completely normal, we would discuss with the patient the alternatives of watchful waiting, empiric cholecystectomy, or ERCP. At ERCP, we would be prepared to obtain a high-quality pancreatogram, perform pancreatic sphincter of Oddi manometry, treat pancreas divisum if identified, and place a pancreatic duct stent at the completion of the procedure. If repeated attacks continued, we would refer the patient to a genetic counselor to discuss the role of genetic testing.

Suggested Reading

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