Chronic Pancreatitis: Making the Diagnosis

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Clinical Scenario

A 38-year-old man with a 10 pack-year smoking history was referred for an evaluation of a 15-year history of recurrent pancreatitis. His first episode of acute pancreatitis occurred after an episode of alcohol binge drinking. He continued to consume moderate amounts of alcohol (8–12 beers/weekend) for 3 to 4 years after his initial attack of pancreatitis. He has not had alcohol in 10 years but continues to smoke and have recurrent episodes of abdominal pain requiring hospitalizations. His admissions are associated with minimal increases in serum lipase level (2–3 × upper limit of normal) and interstitial pancreatitis on computed tomography (CT) imaging. There was one episode of pancreatitis associated with pancreatic necrosis that was without further complications. None of his hospitalizations have been associated with organ failure or intensive care unit admission. He underwent a laparoscopic cholecystectomy several years ago after an ultrasound revealed sludge in the biliary system during one of his acute pancreatitis attacks. Unfortunately, his bouts of pancreatitis have continued and are characterized by a sharp epigastric pain radiating to the back with associated nausea and vomiting. He is now experiencing a mild (3–4 on a 10-point scale), dull, constant abdominal pain between acute pancreatitis attacks, requiring daily narcotic analgesics to control. He was on pancreas enzymes for a short period of time without any noticeable benefit in his pain syndrome. He denies oily or fatty stools.

Does this patient have chronic pancreatitis?

The Problem

Establishing a Diagnosis of Chronic Pancreatitis Can Be Difficult

Chronic pancreatitis should be in the differential diagnosis of a patient with typical features of epigastric pain with radiation to the back, steatorrhea, weight loss, or recurrent acute pancreatitis. Patients generally have known risk factors for chronic pancreatitis such as moderate to heavy alcohol exposure. Because the disease is irreversible and carries a social stigma, the diagnosis needs to be certain before labeling a patient with this chronic illness. Further clinical evaluation is warranted in patients with a high suspicion of disease.

Chronic pancreatitis usually can be divided into several etiologic categories. The most widely accepted etiologic classification system is the Toxic Idiopathic Genetic Autoimmune Recurrent Obstructive system (Table 1), which categorizes risk factors according to mechanism of pancreatic injury.[1] Our patient's history of recurrent pancreatitis (R, recurrent), alcohol abuse, smoking, (T, toxic), and chronic abdominal pain all increase his pretest probability of chronic pancreatic disease.

The radiologic and endoscopic evaluation of a patient with suspected chronic pancreatitis should progress from a least invasive to more invasive approach to establish a diagnosis. Patients with equivocal/borderline imaging findings or refractory symptoms may be referred to specialized centers for additional studies such as secretin-enhanced magnetic resonance imaging (MRI)/secretin-enhanced magnetic resonance cholangiopancreatography (sMRCP) or endoscopic procedures such as endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and pancreas function testing.

The post-test probability of chronic pancreatic disease is determined by the clinical history, physical examination in combination with etiologic risk factors, and results of radiologic and endoscopic imaging tests. Despite exhaustive attempts at diagnosis, up to 5% to 10% of patients cannot be clearly diagnosed with certainty because of disagreement or discordance between imaging and endoscopic findings.

Currently, there are no consensus practice guidelines for the management of chronic pancreatitis. However, appropriate use guidelines for radiologic imaging and gastrointestinal endoscopy have been published by various societies that can be applied to the evaluation of patients with suspected chronic pancreatitis. We have summarized the salient features of these guidelines and introduce a safe (survey tomography/imaging endoscopy pancreas function [STEP]-wise) algorithm to assist in the diagnosis (Figure 1).

Pathophysiology of Chronic Pancreatitis

New insight has been gained into the cellular pathways that lead to the development of chronic pancreatitis.[2] The pathogenesis of chronic pancreatitis appears to result from a series of necrosis-fibrosis events that eventually leads to the chronic inflammation, fibrosis, and scarring seen on histology (sentinel acute pancreatitis event hypothesis). These pathologic changes induce exocrine insufficiency, endocrine dysfunction, and neural inflammation. The clinical features that result from these morphologic changes can include any of the following: abdominal pain caused by neural inflammation, recurrent acute

Abbreviations used in this paper: **CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; sMRCP, secretin-enhanced magnetic resonance cholangiopancreatography; STEP, survey tomography/imaging endoscopy pancreas function.**

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Table 1. TIGAR-O Etiologic Classification of Chronic Pancreatitis

Toxic metabolic
Alcoholic
Tobacco smoking
Hypercalcemia
Hyperlipidemia
Chronic renal failure
Idiopathic
Tropical
Cause unknown; likely genetic
Genetic
Autosomal dominant
Cationic trypsinogen
Autosomal-recessive/modifier genes
CFTR mutations
SPINK1 mutations
α-1-antitrypsin deficiency
Autoimmune
Isolated autoimmune chronic pancreatitis
Associated with the following:
Primary sclerosing cholangitis
Sjogren's syndrome
Primary biliary disorder
Type 1 diabetes mellitus
Recurrent and severe acute pancreatitis
Postnecrotic (severe acute pancreatitis)
Vascular diseases/ischemia
Postradiation exposure
Obstructive
Pancreas divisum (controversial)
Sphincter of Oddi dysfunction (controversial)
Duct obstruction (tumors, post-traumatic)

CFTR, Cystic fibrosis transmembrane conductance regulator; SPINK1, Serine protease inhibitor Kazal-type 1; TIGAR-O, Toxic Idiopathic Genetic Autoimmune Recurrent Obstructive.

pancreatitis as a result of fibrosis and scarring, fatty food intolerance/steatorrhea caused by loss of exocrine function, and glucose intolerance/diabetes as a result of endocrine dysfunction.

Natural History of Chronic Pancreatitis

Chronic pancreatitis generally is characterized by a progressive, irreversible fibroinflammatory process that results in glandular dysfunction and abdominal pain. Epidemiologic studies suggest that chronic intermittent abdominal pain can develop at least 10 to 15 years earlier than parenchymal and ductal changes in hereditary pancreatitis.[3] Other investigators also have reported abdominal pain as the leading symptom in early chronic alcoholic pancreatitis presenting as persistent or intermittent episodes of abdominal pain.[4] Furthermore, pain associated with early idiopathic chronic pancreatitis may present several years before the development of exocrine/endocrine insufficiency.[5] These natural history studies in hereditary, alcoholic, and idiopathic pancreatitis provide supporting evidence that chronic pancreatitis can be characterized by a prodrome of abdominal pain before the development of pancreatic endocrine or exocrine insufficiency. This stage of chronic pancreatitis is impossible to diagnose and characterize with absolute certainty.

Evidence for Use of Radiologic, Endoscopic, and Function Tests in the Diagnosis of Chronic Pancreatitis

There is an exhaustive list of noninvasive (radiologic) and invasive (endoscopic) imaging tests available for the diagnosis of chronic pancreatitis. Radiologic studies include abdominal CT scan and MRI, and endoscopic tests include EUS, and in some cases ERCP. Some centers such as ours perform direct pancreas function tests.[6] We briefly discuss important facts about each procedure as they relate to chronic pancreatitis. Most published diagnostic criteria are based on the initial Cambridge classification system for ERCP, which has had several modifications over the years.[7–9] Table 2 presents the most common accepted chronic pancreatitis diagnostic criteria for radiologic (CT and MRI/MRCP) and endoscopic (EUS, ERCP) imaging studies.

Computed tomography. According to the American College of Radiology Appropriateness Criteria,[10] ultrasound or computed tomography usually is appropriate in the evaluation of patients presenting with upper abdominal pain (grade 3 recommendations; modified Delphi technique; rating scale 6–8; expert opinion). Although ultrasound is noninvasive and safe, overlying bowel gas limits its ability to completely visualize the pancreas. A contrast-enhanced CT is usually the initial method of choice in the evaluation of the pancreas. CT is usually normal in early or minimal change chronic pancreatitis, but should be performed in all patients to exclude a mass or gastrointestinal malignancy. CT is only definitive for chronic pancreatitis when moderate and marked changes of calcifications, duct irregularity, or fluid collections in pancreatic morphology are present (Figure 2 illustrates the definitive features of chronic pancreatitis, which may be seen on CT imaging according to Cambridge criteria[7–9]). Most centers will perform a pancreas protocol CT that provides better imaging resolution of the gland.

Magnetic resonance imaging, magnetic resonance cholangiopancreatography, and secretin-enhanced magnetic resonance cholangiopancreatography. MRI rapidly is emerging as the initial radiologic imaging modality of choice for the evaluation of chronic pancreatitis at specialized centers in patients with an equivocal or borderline CT scan.[11–15] Guidelines from the American College of Radiology[16] state that magnetic resonance imaging is usually (increased pancreas enzyme levels) or may be (pain only) appropriate in the evaluation of abdominal pain of possible pancreas origin (grade 3 recommendations; modified Delphi technique[17]; rating scale 6–8; expert opinion). Combined use of MRI and MRCP can reveal both parenchymal and ductal findings that are associated with chronic pancreatitis. The addition of sMRCP can further assist in the evaluation of subtle changes in the pancreatic duct side branches, main ductal compliance, and duodenal filling.[18,19] Definitive diagnosis of chronic pancreatitis can be made with certainty only by MRI/MRCP when both the main duct and side branches show moderate to marked alterations similar to that seen on a retrograde pancreatogram. Figure 3 shows pancreatogram changes consistent with chronic pancreatitis on sMRCP. It should be kept in mind, however, that no consensus has been reached concerning the grading of MRI/MRCP according to the Cambridge criteria.[20] Furthermore, the value of low signal intensity, ductal compliance, and rapidity of duodenal filling after secretin stimulation is currently unknown but is under investigation.

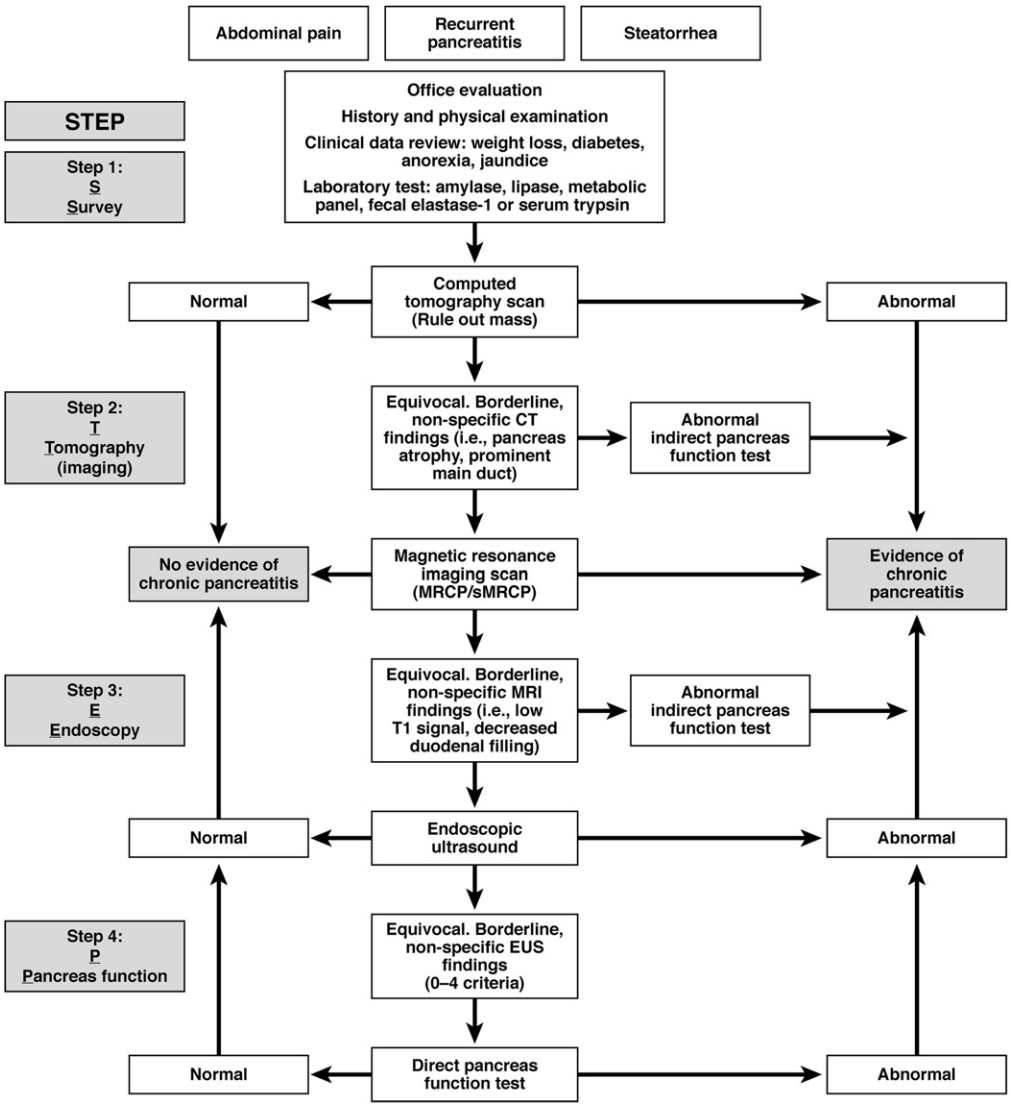

Figure 1. STEP-wise algorithm for the diagnosis of chronic pancreatitis.

Endoscopic ultrasound. The American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy have published guidelines to establish quality indicators for EUS[21] and ERCP.[22] These guidelines are grade 3 recommendations, which are a result of systematic reviews and expert opinion.[23] EUS provides excellent parenchymal and ductal visualization of the pancreas.[24–26] Endosonographic diagnostic criteria for chronic pancreatitis have been developed and new scoring systems are continuing to be developed. Figure 4 displays some of the more common endosonographic features observed in chronic pancreatitis.[27] Both acinar- and duct-cell function decrease as EUS structural abnormalities increase.[28,29] Clinical symptoms suggestive of pancreatic disease also appear to be correlated with ductal abnormalities.[30] At least 5 standard EUS criteria are needed before a diagnosis of chronic pancreatitis can be made definitively.[29,31] The meaning of less than 4 EUS criteria is uncertain. Some findings initially believed to be suggestive of chronic pancreatitis have been described in asymptomatic patients and seem to be associated with normal aging, smoking, obesity, or alcohol consumption.[32–34]

Endoscopic retrograde cholangiopancreatography. Criteria for chronic pancreatitis on retrograde pancreatogram traditionally have been based on the Cambridge classification system.[7–9] In general, the degree of pancreatic ductal abnormalities correlates with the degree of disease severity and exocrine dysfunction. The advent of MRI/MRCP and EUS have obviated the need and risk associated with diagnostic ERCP for chronic pancreatitis.[35] Current American Society of Gastrointestinal Endoscopy guidelines recommend that ERCP be reserved for those patients in whom the diagnosis of chronic pancreatitis has not been established by noninvasive or less-invasive studies.[36] The guidelines further state that diagnostic ERCP should not be undertaken in the evaluation of pancreaticobiliary pain in the absence of objective clinical or radiographic findings. Most centers only perform ERCP when therapeutic intervention (sphincterotomy, sphincter of Oddi manometry) is being considered.

Direct and indirect pancreas function tests. Chronic inflammation and scarring in the pancreas decreases acinar as well as duct cell secretory function.[29] Dysfunction caused by chronic pancreatitis can be determined by indirect or direct measurement of specific concentrations of cellular

Table 2. Definite Chronic Pancreatitis Morphologic Criteria

CT criteria
Moderate pancreas changes, ≥2 of the following:
Main duct enlarged (2–4 mm)
Slight gland enlargement (up to 2× normal)
Heterogenous parenchyma
Small cavities (<10 mm)
Irregular ducts
Focal acute pancreatitis
Increased echogenicity of the main pancreatic duct wall
Irregular head/body contour
Marked pancreas changes: as described earlier, with ≥1 of the following:
Large cavities (>10 mm)
Gross gland enlargement (2× normal)
Intraductal filling defects or pancreatic calculi
Duct obstruction, stricture, or gross irregularity
Contiguous organ invasion
MRI/sMRCP criteria[a]
Moderate pancreatogram changes
Main duct abnormal and
Abnormal side branches, >3
Marked pancreatogram changes
Main duct abnormal and
Abnormal side branches, >3
Plus one or more of the following:
Large cavity
Obstruction
Filling defects
Severe dilatation or irregularity
Endoscopic ultrasound criteria
Parenchymal pancreas abnormalities (n = 4)
Hyperechoic foci
Hyperechoic strands
Lobular contour
Cysts
Ductal pancreas abnormalities (n = 5)
Main duct dilation
(>3 mm head; >2 mm body; >1 mm tail)
Duct irregular
Duct hyperechoic margins
Visible side branches
Stones
ERCP criteria
Moderate pancreatogram changes
Main duct abnormal and
Abnormal side branches, >3
Marked pancreatogram changes
Main duct abnormal and
Abnormal side branches, >3
Plus one or more of the following:
Large cavity
Obstruction
Filling defects
Severe dilatation or irregularity

[a]Although MRI and sMRCP imaging findings are similar to CT and ERCP, respectively, it should be noted that Cambridge-type criteria have not been established for MRCP. The diagnostic accuracy of other features of MRI such as alterations in signal intensity and diffusion-weighted imaging is under investigation and represents areas of uncertainty.

secretory components in pancreatic fluid, serum, or stool. Fecal measurement of pancreatic elastase-1 or serum measurement of trypsin are indirect measures of pancreas function that are ordered primarily during the office evaluation. Most studies have shown that pancreatic exocrine insufficiency does not develop clinically (steatorrhea) until greater than 90% of the gland has been scarred or fibrosed.[37] Indirect pancreas function tests such as elastase-1 measurements in stool and serum trypsin concentrations are abnormal when the patient has marked degrees of exocrine dysfunction. Direct pancreas function tests using secretin or cholecystokinin stimulation are advantageous because they can detect abnormalities in pancreas fluid secretion before the development of steatorrhea or definite radiologic abnormalities as described earlier. Thus, pancreatic secretory dysfunction as measured by a direct pancreas function test is considered an early marker of chronic pancreatitis.

Although direct function testing has been available for more than 70 years, it has been greatly underused owing to the complexity of pancreas fluid collection.[38] Endoscopic modifications such as the endoscopic pancreatic function test method have made the test more available.[39–42] Figure 5 is the endoscopic appearance of the duodenum filled with pancreas fluid after hormonal stimulation with cholecystokinin or secretin. This fluid can be aspirated and analyzed to determine secretory function of the pancreas.

A Combined Diagnostic Testing Approach to Chronic Pancreatitis Diagnosis

Figure 1 displays a diagnostic algorithm that proceeds from a noninvasive to invasive diagnostic approach for chronic pancreatitis based on established imaging criteria. We also have shown where pancreas function testing can be most useful in patients with persistent symptoms and nonspecific imaging findings. Our (STEP-wise) approach is to survey all clinical data

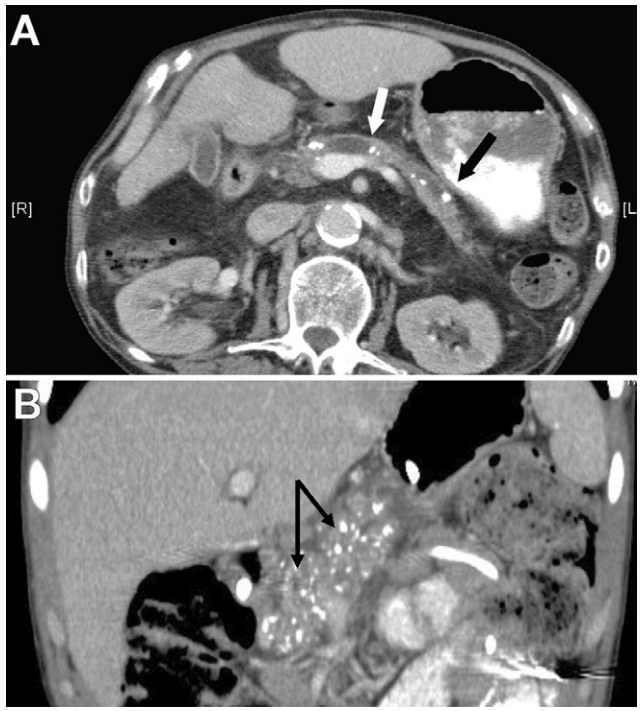

Figure 2. CT chronic pancreatitis (Cambridge, marked changes). (*A*) Pancreatic calcifications (*black arrow*); marked pancreatic ductal dilation (10 mm) and glandular atrophy (*white arrow*). (*B*) Diffuse pancreatic calcifications in head, neck, and body of pancreas (*black arrows*, coronal view).

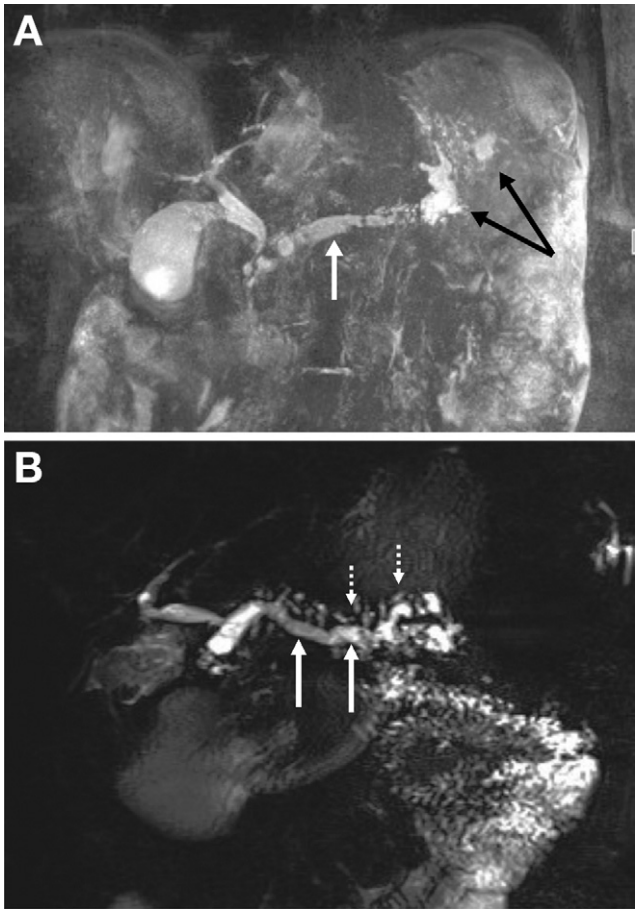

Figure 3. sMRCP chronic pancreatitis (Cambridge, marked changes). Diffuse dilatation of the pancreatic duct and multiple side branches, consistent with chronic pancreatitis. (*A*) Dilatation of the main pancreatic duct in the body and tail (*white arrow*). Pseudocysts are identified in the tail of the pancreas (*black arrows*). (*B*) Dilated main duct with areas of absent signal likely represents calcification and debris (*white arrows*). Abnormal pancreatic duct side branches (*dashed white arrows*). There was no significant change in the caliber of the main pancreatic duct after the administration of secretin, suggesting scarring and fibrosis of the duct. Pancreas fluid is seen in the small bowel after secretin stimulation.

and review outside radiologic studies with an abdominal imaging radiologist. Laboratory tests including an amylase, lipase, metabolic panel, and fecal elastase-1 or serum trypsin are generally ordered. Radiographic (tomography/imaging) studies, including a pancreas protocol CT scan followed by an MRI/MRCP if necessary, are performed to assess for definitive changes of chronic pancreatitis and rule out a pancreas mass. If the diagnosis is not confirmed on abdominal imaging, the evaluation usually proceeds to more invasive advanced endoscopy procedures and direct pancreas function testing. Moderate to marked changes on pancreas imaging or endoscopy as outlined in Table 2 are diagnostic for chronic pancreatitis. Borderline findings in combination with a positive indirect or direct pancreas function test also confirms the diagnosis of chronic pancreatitis.

Areas of Uncertainty

There have been major advances in radiographic and endoscopic imaging resolution. Unfortunately, the inability to safely obtain a histologic gold standard biopsy has markedly limited our ability to accurately assess the significance of these findings. Therefore, the numerous morphologic changes that are described on EUS, MRI, and sMRCP are difficult to interpret in regards to early diagnosis. Furthermore, very few studies exist that compare function testing with histology.

EUS is very sensitive at detecting structural abnormalities in the pancreas. As described previously, these findings may not necessarily be related to chronic pancreatitis. Recent studies also have suggested some endosonographic abnormalities may be better predictors of early disease.[29] The new Rosemont scoring system is under current clinical research investigation and early reports suggest it may be no better than the current diagnostic criteria.[27,35]

The ability of MRI/MRCP to detect chronic pancreatitis is also an area of active investigation. The significance of signal enhancement and the secretory dynamic changes (duct compliance, rapidity of duodenal filling) that occur after secretin stimulation need further study. Standardization of MRI reports and nomenclature is needed to improve communication between centers and develop uniform criteria for diagnosis. Development of a scoring system is needed for MRCP similar to the Cambridge score in ERCP.[43] Early reports of diffusion-weighting MRCP are promising and also may enhance the diagnostic accuracy of chronic pancreatitis.[44]

Preoperative function test results are being compared with histologic findings from total pancreatectomy subjects and the results are promising.[45] Although moderate dosages of conscious sedation used in endoscopic function testing do not effect pancreas secretion to a great degree; the effects of large dosages of narcotics and general anesthesia required to sedate some chronic pain patients is unknown. Until further evidence is available, borderline direct pancreas function test results in these patients should be interpreted with caution.

Finally, incorporation of advanced molecular biotechnology techniques such as proteomics, genomics, and cell biology into translational pancreatic disease research may further improve our understanding of the molecular pathways involved in the pathogenesis of chronic pancreatitis.[46–50] This may lead to the development of diagnostic biomarkers that can clarify equivocal and borderline findings in patients with suspected chronic pancreatic disease.

Published Guidelines

Unlike acute pancreatitis, in which there are many published recommendations; there is a lack of published clinical practice guidelines for chronic pancreatitis.

Appropriateness criteria and quality indicators from the American College of Radiology,[10,16] the American College of Gastroenterology, and the American Society of Gastrointestinal Endoscopy have been outlined previously.[21,22,36,51,52] Furthermore, there are numerous proposed international etiologic and clinical classification systems for chronic pancreatitis that describe diagnostic criteria within their proposed systems.[1,53–58] The M-ANNHEIM (2007), German (2009), and Revised Japanese (2010) systems are the most recent published reports to date.[20,59,60] A universal consensus document or practice guideline has not been published for chronic pancreatitis.

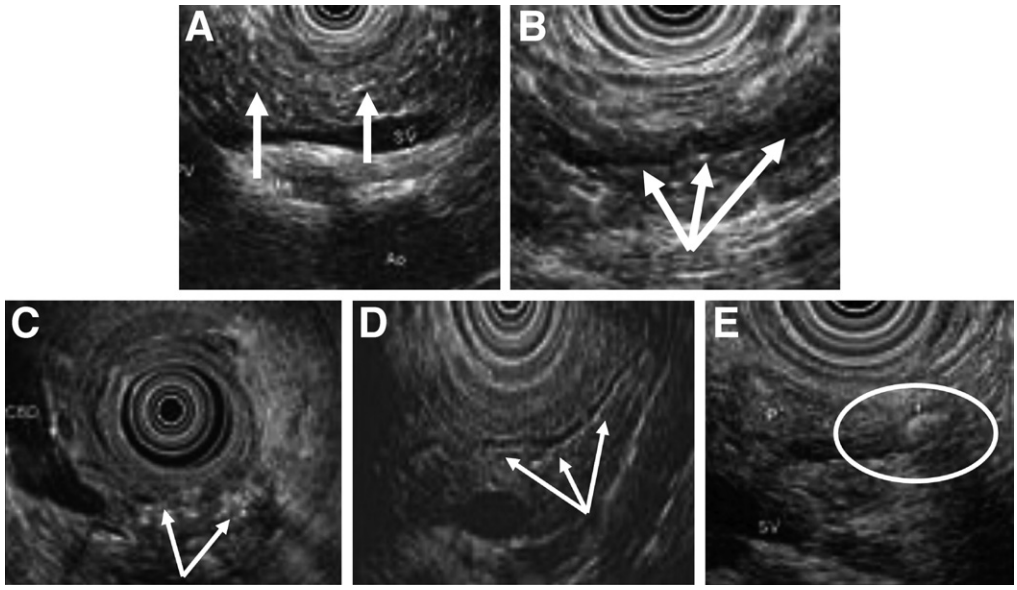

Figure 4. Commonly described EUS chronic pancreatitis criteria. (*A*) Hyperechoic strands. (*B*) Hyperechoic duct wall. (*C*) Parenchymal calcifications. (*D*) Irregular hyperechoic duct. (*E*) Pancreatic duct stone.

Recommendation for This Patient

Our patient's pain is constant and is poorly controlled on oral narcotic medication. He has a moderate history of alcohol and is a 10-pack/year smoker. He has epigastric tenderness on examination and there are no signs of alcoholic liver disease. We had a strong clinical suspicion for chronic pancreatitis (high pretest probability of disease) that warranted further investigation. Outside imaging was reviewed with our abdominal imaging radiology staff and showed changes of acute pancreas inflammation and interstitial pancreatitis. Serum laboratory studies were normal and the fecal elastase-1 measurement was 205 μg/g (normal, >200 μg/g). A pancreas protocol CT scan revealed pancreas atrophy and a focal hypodense area within the body of the pancreas measuring 2.3 $\times$ 0.9 cm. An MRI revealed decreased signal intensity throughout the pancreas and changes of fibrosis and scarring that corresponded to the previously described hypodense lesion in the pancreatic body. The MRCP/sMRCP portion of the examination revealed no dilatation of the intrahepatic or extrahepatic bile ducts. The pancreatic duct showed normal caliber throughout, without evidence of stricture. There were no filling defects seen. An endoscopic ultrasound revealed pancreatic parenchymal abnormalities in the entire pancreas. These consisted of hyperechoic strands and hyperechoic foci. The main pancreatic duct had hyperechoic walls and measured up to 2 mm in diameter (nondilated). In total, there were 3 chronic pancreatitis EUS criteria. A direct pancreas function test with secretin stimulation was performed to clarify the earlier-described imaging findings and our strong clinical suspicion for chronic pancreatitis.[41] The peak duodenal fluid bicarbonate after secretin stimulation was 53 mEq/L (normal, >80 mEq/L). This is positive for pancreas secretory dysfunction and is considered an abnormal test result that is seen in chronic pancreatitis.

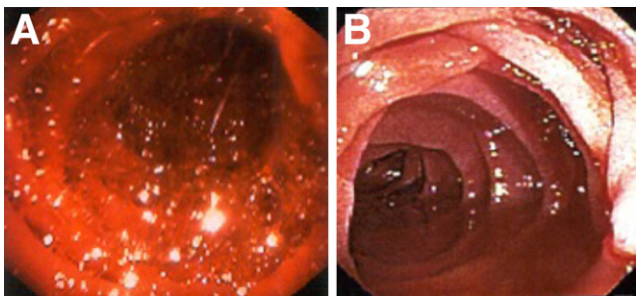

Figure 5. Direct pancreas function test. Endoscopic view of the duodenum after cholecystokinin (*A*) or secretin (*B*) stimulation of the pancreas.

Final Diagnosis: Chronic Pancreatitis

Based on the earlier-described comprehensive evaluation of pancreatic morphology, ductal anatomy, and secretory function, it was determined that our patient had evidence to support a diagnosis of chronic pancreatitis. Traditionally, the nonspecific nomenclature used to describe his disease would be "small duct" or "minimal change" chronic pancreatic disease. This patient's chronic pancreatitis would be better classified as probable chronic pancreatitis using the M-ANNHEIM (multiple risk factor classification: alcohol consumption, nicotine consumption, nutritional factors, hereditary factors, efferent pancreatic duct factors, immunological factors, and rare miscellaneous and metabolic factors) and Revised Japanese diagnostic criteria or stage-A chronic pancreatitis in the German A, B, C classification system.

Conclusion

We have presented a safe (STEP-wise) approach to the diagnosis of chronic pancreatitis that uses the most commonly available radiographic and endoscopic tests. The diagnosis of chronic pancreatitis should be made based only on established criteria. We have shown how the addition of pancreatic function testing to standard radiologic and endoscopic imaging can assist in the evaluation of these sometimes perplexing patients with equivocal or borderline imaging findings.

Until better diagnostic tests or biomarkers of chronic pancreatitis are available, patients with continued symptoms and equivocal/borderline findings should undergo serial testing

(MRI, pancreas function testing, EUS) to assess for chronic pancreatitis or an occult gastrointestinal neoplasm.

Extreme caution should be taken not to mislabel patients with a diagnosis of chronic pancreatitis when in fact they have a chronic abdominal pain syndrome and a remote history of procedure (ERCP)-induced pancreatitis.

Consensus practice guidelines are under development in chronic pancreatitis similar to those available in acute pancreatitis. The M-ANNHEIM, German, and Revised Japanese clinical diagnostic criteria provide a platform from which to build a system that allows patients to be categorized according to etiology, clinical stage, and severity of their disease. This will greatly advance not only clinical research but our ability to care for patients with this often debilitating disease.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.