Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done?

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INTRODUCTION

Acute recurrent pancreatitis (ARP) is a common, potentially life-threatening condition that requires a combination of sophisticated medical and interventional skills to diagnose, determine the etiology and treat. After an initial episode of pancreatitis studies suggested that 30% of the patients will become experience recurrence[8], the etiology of ARP has been evaluated in a number of classic studies with alcohol and gallstones were found to be the major contributors[9-11], accounting for 70% of the cases.

According to Tandon et al[8], “idiopathic acute pancreatitis” was defined as pancreatitis with no etiology established after initial laboratory (including lipid and calcium level) and imaging (either transabdominal ultrasound and/or CT scan) tests. However, there is no consensus on the duration of an “acute attack”, as pancreatic parenchymal changes such as edema and fluid collection may persist after the complete normalization of pancreatic enzymes and resolution of patient’s symptoms. The definition is less specific if the interval between the acute attacks is short, where inflammation and edema may persist. For the purposes of this discussion, we will define acute pancreatitis according the Atlanta Symposium[9] as an acute inflammatory process of the pancreas, usually associated with severe pain in the upper abdomen with a 3-fold rise in amylase and lipase. ARP is defined as at least 2 episodes of acute pancreatitis with complete or near complete resolution of symptoms and signs of pancreatitis between episodes.

DIAGNOSTIC EVALUATION

ARP remains a diagnostic dilemma. It is estimated that 10% of a single pancreatitis cases and up to 30% of recurrent pancreatitis remain undiagnosed after history, laboratory testing, and routine imaging[12-13].

Initial laboratory testing should include serum calcium and triglycerides. Although an uncommon complication, hypercalcemia of any cause can lead to acute pancreatitis[14-15]. Suggested mechanisms include deposition of calcium in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma[16]. Serum triglyceride concentrations above 1000 mg/dL (11 mmol/L) can precipitate attacks of acute pancreatitis[17], although the mechanism of inflammation in this case remains unclear.
The combination of bile crystal analysis and endoscopic retrograde cholangiopancreatography (ERCP) with or without sphincter of Oddi manometry (SOM) has led to identifying the underlying etiology up to 76% of cases of otherwise unexplained acute pancreatitis[12,13]. The advent of EUS and the rapid evolution of various imaging modalities have provided a less invasive highly accurate alternative for studying the pancreas and the biliary tree. In this review, we will focus on the diagnostic approach to patients with ARP including medical testing, imaging and endoscopy.

**EUS OR ERCP?**

ERCP has been used for decades in the evaluation of idiopathic recurrent pancreatitis. The role of ERCP emerged prominently in the diagnosis of underlying cholelithiasis[12,13], papillary stenosis[14], pancreas divisum[15] and sphincter of Oddi dysfunction[1]. The major limitation of ERCP is the risk of inducing acute pancreatitis, which may be as high as 20% in patients being evaluated for SOD and is 5%-6% in the general population[19]. Over the past 10 years, EUS has replaced ERCP for most diagnostic evaluations due to its high accuracy (at least for bile duct stones, tumors, pancreas divisum and cysts) and lower risk of complications[18]. The major limitation of EUS is the inability to clearly diagnose SOD.

Coyle et al[17] studied the diagnostic utility of ERCP with SOM, bile analysis and EUS in patients with acute and ARP. A diagnosis was found in the majority of the cases (80%), where SOD was the most common finding (31%), while pancreatic divisum was found in 20% of patients. EUS was very useful in the diagnosis of biliary diseases and detected all tumors. Endoscopic ultrasound (EUS) was able to identify 9 patients with chronic pancreatitis, which ERCP did not identify. However, EUS was not able diagnose any patient with SOD.

In a similar study by Fossard et al[17] EUS identified the cause of acute pancreatitis in 77% of patients. EUS was abnormal EUS were compared with other investigations, EUS correctly identified the cause of the “idiopathic” pancreatitis in 155 (92%) of the patients, most commonly being biliary tract disease. EUS missed the diagnosis in 5 patients with biliary stones and one patient with intraductal papillary mucinous neoplasm (IPMT). The authors concluded that EUS is valuable in determining the cause of acute pancreatitis in patients initially considered to have idiopathic pancreatitis.

According to Tandon et al[15], EUS was successful in determining the etiology of idiopathic acute pancreatitis in 21 out of 31 patients (68%). The diagnoses made by EUS were: chronic pancreatitis (43%), microcystic (16%), pancreatic divisum (6.5%) and pancreatic carcinoma (3.2%), and was not diagnostic in 10 (32%) The mean follow up was 16 mo. Thirteen patients in this study had further recurrent pancreatitis or pancreatic symptoms and underwent further investigations. Only nine of these patients required ERCP and four patients had a change of their previous EUS diagnoses. Hence, 87% (27 of 31 patients) of the initial EUS diagnoses were unchanged at the end of follow up. Two patient groups were included in this study and provoked criticism: patients with significant alcohol consumption and patients with only single episode of pancreatitis.

A prospective study of 300 patients of single episode and recurrent pancreatitis by Yusoff et al[16] concluded that it is reasonable to perform EUS after the first episode of pancreatitis. Diagnostic yield of EUS was comparable between the 2 groups (single vs recurrent episodes). Patients with significant alcohol intake and with features of chronic pancreatitis were excluded from this study.

**WHEN CAN EUS REPLACE ERCP?**

The most likely area where EUS can replace ERCP, at least as the initial diagnostic test, is when biliary tract disease such as stones, are suspected. Prat et al[19] studied the value of early EUS to avoid unnecessary cannulation of the bile duct in patients with acute biliary pancreatitis. ERCP was only performed if biliary stones were seen by ERCP. There were no false positive EUS results and no EUS related complications. Also, Napoleon and his colleagues[20] found that the negative predictive value of EUS for the diagnosis of CBD stones was 95.4%. Therefore, they concluded that EUS should effectively replace ERCP as the initial diagnostic test of choice.

Two other studies also examined the utility of EUS in idiopathic pancreatitis suspected to be of biliary origin. Norton and Alderson[21] found that pancreato-biliary causes of idiopathic acute pancreatitis can be established in at least 18 of 44 patients (41%) studied. Although this diagnostic yield is lower compared with 68% suggested by Tandon[15], patients with significant alcohol intake were excluded in the Norton study. In addition, Liu et al[22] found that EUS led to the correct diagnosis in 14 of 18 patients (78%) with idiopathic pancreatitis of choledocholithiasis and/or cholecystitis. Although this study excluded patients with history of excess alcohol ingestion, it included patients with only one episode of pancreatitis. As for IPMT, EUS has a sensitivity of 86% and specificity of 99% in diagnosing IPMT[23].

Autoimmune pancreatitis (AIP) is a rare but increasingly diagnosed clinical entity[24,25], which can present as pancreatic or biliary strictures, acute recurrent pancreatitis or even pancreatic mass. Elevated serum levels of IgG4 provide a strong marker for the disease[26,27]. Serum IgG4 accounts for only 5 to 6 present of the total IgG in healthy subjects but is elevated in patients with AIP. A large study by Hamano et al[25] compared serum IgG4 levels in 20 patients with AIP with 20 healthy controls, and 154 patients with a variety of malignant and non-malignant pancreatic diseases. The median serum IgG4 concentration in patients with AIP was 663 mg/dL compared with 51 mg/dL in healthy controls. The serum IgG4 concentrations in the other group of patients were similar to those in healthy subjects with no values above 135 mg/dL. Using a cutoff of 135 mg/dL, the sensitivity and specificity of the serum IgG for distinguishing AIP from pancreatic cancer were 95 and 97 percent, respectively. Levels of IgG4 declined during treatment with corticosteroids. Classic endosonographic features include diffusely hypoechoic, enlarged pancreas together
with chronic inflammatory cells on aspirated cytologic specimens. However, EUS fine needle aspiration (FNA) is usually insufficient to diagnose autoimmune pancreatitis due to the small sample size and lack of tissue architecture. In a study by Levy et al., five patients in whom the diagnosis was considered were evaluated. A mean of 2.8 EUS truecut biopsy (range 2-5) was obtained per patient.

Truecut biopsy specimens were diagnostic of AIP in two patients and were strongly suggestive but not diagnostic in two others. In one patient only nonspecific changes of chronic pancreatitis were seen on histology. EUS FNA (mean 4.3 passes, range 2-7 passes) was performed in four of five patients and failed to establish or suggest the diagnosis in any of these patients. Serum IgG4 and EUS should be considered first line tests in cases where AIP is suspected.

A major advantage of ERCP compared to EUS is the ability to perform manometry and, if needed, intervention if specific etiologies have been found in the same setting. For the common causes found in patients with unexplained pancreatitis, sphincterotomy (either biliary or pancreatic) or stent insertion could be performed. To overcome this disadvantage, Rocca et al. recently presented a prototype oblique-viewing echoendoscope capable of performing EUS and ERCP in the same session. Nineteen patients with acute abdominal pain associated with increased liver tests entered the study and underwent EUS. When biliary stones or sludge were found, bile duct cannulation and sphincterotomy were performed in the same session. Bile duct cannulation failed in only one patient and no procedure-related complications were observed. The authors concluded that this approach was accurate, safe and feasible for the treatment of common bile duct stones when needed. Further larger studies are needed to confirm these findings.

MRCP

MRCP represents a very useful radiographic tool for the assessment of the intra and extrahepatic biliary tree and pancreatic duct. In the recent years, the concurrent use of secretin makes MRCP an attractive first line test for ARP to assess for structural underlying etiologies. Until recently, sphincter of Oddi evaluation remained almost completely dependent on endoscopic approach. However, a study by Mariani et al. compared secretin MRCP and pancreatic sphincter of Oddi manometry for evaluation of sphincter of Oddi function in patients with idiopathic ARP. Eighteen patients and a similar number of controls underwent both tests and data from 15 patients was available for analysis. Secretin MRCP and sphincter of Oddi manometry were concordant in 13/15 patients (86.7%); positive and negative diagnoses for sphincter of Oddi dysfunction agreed in, respectively, 81.8% and 100% (kappa value 0.706).

Another study by Khalid et al. evaluated pancreatic duct outflow obstruction in cases of idiopathic ARP. Ten patients with idiopathic acute recurrent pancreatitis underwent secretin-stimulated magnetic resonance pancreatography with subsequent endoscopic retrograde pancreatogram with or without manometry. It was found that secretin stimulated magnetic resonance pancreatography provides high quality pancreatic duct images and has high specificity for diagnosing pancreatic duct outflow obstruction using manometric and clinical criteria.

GENETIC TESTING

Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations were noted to be associated with cystic fibrosis (CF)-related conditions, including idiopathic recurrent pancreatitis in otherwise non-symptomatic patients. A prospective study by Bishop et al. included idiopathic ARP, healthy controls, CF heterozygotes, and CF patients (pancreatic insufficient or sufficient) for evidence of CFTR gene mutations. At least one CFTR mutation or variant was carried in 6 of 16 patients (38%) with idiopathic ARP but in only 11 of the 50 controls (22%, P = 0.005). Identified mutations were rare and not usually identifiable with the routine screening test. While genetic testing may carry more significance in the diagnostic work up of chronic pancreatitis, acute pancreatitis can be viewed as an event that leads to the process of chronic pancreatitis. The role of other mutations involving cationic trypsinogen (PRSS1) and in serine protease inhibitor Kazal type 1 (SPINK1) genes seen in idiopathic chronic pancreatitis is less established in ARP and further studies are required.

CONCLUSION

Each of the above-described modalities to diagnose ARP has its pros and cons. Despite the fact that there are limitations in using EUS to investigate ARP, it remains a reasonably accurate and less invasive alternative to ERCP for patients with only one episode of pancreatitis. For certain cases of recurrent pancreatitis, besides being able to perform interventions, ERCP offers additional information about sphincter of Oddi function, and also in cases of pancreas divisum where the sensitivity and specificity of EUS needs further evaluation. In other cases where biliary stones or IPMT are suspected, EUS remains a less invasive and equally accurate test of choice. The risks and benefits of these procedures should be individually evaluated in each case. MRCP with secretin stimulation is a non-invasive, promising tool but requires advanced interpretation skills and may not be widely available. In a subset of patients where structural causes have been ruled out, genetic testing may be helpful in the appropriate clinical set-up.

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