World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i4.107

World J Gastrointest Endosc 2010 April 16; 2(4): 107-111
ISSN 1948-5190 (online)

EDITORIAL

Endoscopic ultrasonography and idiopathic acute pancreatitis

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Received: March 13, 2009 Revised: March 31, 2010
Accepted: April 7, 2010
Published online: April 16, 2010

Abstract

Idiopathic acute pancreatitis is a diagnostic challenge for gastroenterologists. The possibility of finding a cause for pancreatitis usually relies on how far the diagnostic study is taken. Endoscopic explorations such as endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography can help to determine the cause of pancreatitis. Furthermore, microscopic bile examination and magnetic resonance cholangiopancreatography can also be helpful in the work up of these patients. In this article an approximation to the diagnostic approach to patients with idiopathic acute pancreatitis is made, taking into account the reported evidence with which to choose between the different available explorations.

Key words: Endosonography; Cholangiopancreatography; Endoscopic retrograde; Cholangiopancreatography; Magnetic resonance; Microscopic bile examination; Idiopathic pancreatitis; Acute; Diagnosis

Peer reviewers: Everson Luiz de Almeida Artifon, MD, PhD, FASGE, University of Sao Paulo School of Medicine, Rua Guimaraes Passos Zc-04107030, Brazil; Claus Schäfer, Assistant Professor of Internal Medicine/Gastroenterology, Medical Clinic Ⅱ - Campus Grosshadern, University of Munich, Munich 81377, Germany

Vila JJ. Endoscopic ultrasonography and idiopathic acute pancreatitis. *World J Gastrointest Endosc* 2010; 2(4): 107-111 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i4/107.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i4.107

INTRODUCTION

Acute pancreatitis might be defined as an inflammatory process of the pancreas clinically characterized by upper abdominal pain and elevated levels of pancreatic enzymes in the blood. In up to 10% of patients with a single episode of acute pancreatitis and in 30% of patients with acute recurrent pancreatitis, the aetiology is not found after the initial examination. Initial work up should include a detailed clinical history with records of recent infectious diseases, abdominal traumas or surgery; personal records of systemic diseases and ethanol or medicine intake; serum calcium, triglycerides levels, liver enzymes and autoantibodies (ANA, IgG4, rheuma factor); and at least one transabdominal ultrasonography although two are advisable. These patients are diagnosed with idiopathic acute pancreatitis (IAP)[1,2].

This situation represents a diagnostic challenge since in many cases the possibility of finding a cause for the pancreatitis depends directly on how deep the etiological search is made. Thus, when more accurate explorations are performed, gallbladder microlithiasis, sphincter of Oddi dysfunction, pancreas divisum or chronic pancreatitis is usually found. Less commonly, pancreatic tumours or cysts, anatomic anomalies such as a long pancreatobiliary junction (> 15 mm), annular pancreas, choledococele, a duodenal duplication cyst and a periampullary diverticulum can also be found as the cause of the acute pancreatitis bout. In the absence of mechanical and anatomic causes of acute pancreatitis in patients under 40 years of age, gene mutations such as mutations of the cationic trypsinogen gene, in the serine protease inhibitor Kazal type Ⅰ or in cystic fibrosis gene must be considered as a possible cause of the IAP.

Autoimmune pancreatitis, a pancreatic disorder characterized by imaging criteria (enlargement of the pan creatic gland, diffuse narrowing of Wirsung duct with an irregular wall), laboratory criteria (elevation in IgG4 serum levels and positive autoantibodies) and histopa thologic criteria (marked lymphoplasmacytic infiltration and dense fibrosis)[3] has been more frequently diagnosed recently. Using a cut off value of 135 mg/dL, the sensitivity and specificity of the serum IgG4 for distinguishing autoimmune pancreatitis from pancreatic cancer are 95% and 97% respectively[4]. Recent studies indicate that two different types of AIP exist: Type I which is predominantly found in Western Europe and the United States (IgG4 negative) and Type II which is more frequently found in Asia[5,6].

It is of great importance to identify the cause of pancreatitis because if it is not corrected recurrence is common; up to 70% depending on the cause[7]. Moreover, the mortality rate for acute pancreatitis is between 4% and 9% but can be higher for IAP[8].

In order to find the cause of the IAP, several explorations such as Endoscopic Retrograde Cholangio-Pancreatography (ERCP), Magnetic Resonance Cholangio-Pancreatography (MRCP), Microscopic Bile Examination (MBE) or Endoscopic Ultrasonography (EUS) can be performed. By performing one of these explorations or a combination, an etiological diagnosis can be made in up to 90% of cases of IAP.

However, some considerations must be made regarding the etiological diagnosis of patients with IAP.

WHAT THE FIRST LINE DIAGNOSTIC EXPLORATION IN PATIENTS WITH IAP SHOULD BE: ERCP *vs* MBE *vs* EUS *vs* MRCP

ERCP has been the first choice of diagnostic procedures in these patients for over three decades with a diagnostic yield of up to 80% but with a rate of potentially severe complications of 10%-15%[9,10]. An important advantage of ERCP is that it is possible to perform therapeutic manoeuvres necessary in up to 75% of these patients. Taking into account its morbidity rate, some authors recommend an ERCP only after the second episode of IAP or after the first in severe IAP[7,11]. Other authors support the indication of ERCP systematically after the first episode of IAP[12].

In patients with gallbladders, the most frequent cause of the IAP is microlithiasis which is present in up to 80% of these patients[2,13]. The exploration considered as the gold-standard to diagnose microlithiasis is currently the MBE[14] with a sensitivity of 65%-90% and a specificity of 88%-100%[15]. However, this exploration has some drawbacks which should be noted. In 29%-50% of patients with known gallbladder lithiasis, the MBE is falsely negative[16]. Moreover, it is a time consuming exploration which might take up to one hour. It is also not feasible in up to 20% of patients due to it being impossible to place the nasoduodenal probe in the second duodenal portion, aspiration of inadequate material or the patient's intolerance. This rate of exploration failure has also been reported by other groups[17].

Dahan *et al*[18] compared the diagnostic accuracy of EUS with MBE in detecting microlithiasis in patients with IAP or abdominal pain mimicking a biliary colic with transabdominal ultrasonography within normal limits. Results were significantly better with EUS compared to MBE.

However, to my knowledge, these results have not been confirmed by other groups. In a prospective blinded comparative study, we found similar accuracies for EUS and MBE (100% *vs* 95%, $P > 0.05$) in diagnosing the presence of microlithiasis but EUS diagnosed the presence of other pancreatic diseases which could be responsible for the acute pancreatitis bout in 25% of patients[19]. Therefore, MBE should not be currently considered as a first line procedure in the examination of patients with IAP.

Recently EUS has proved to have a diagnostic accuracy between 60% and 80%[20-27] in patients with IAP similar to ERCP but with a lower complication rate comparable to gastroscopy[28]. This gives an idea of the clinical impact of EUS on the management of these patients. Theoretically, with EUS we might be able to diagnose the majority of possible causes of IAP stated previously. Besides the high diagnostic accuracy for detecting gallbladder lithiasis and microlithiasis[29], EUS is considered one of the most accurate techniques in diagnosing chronic pancreatitis[30]. The presence of at least 5 endosonographic criteria of chronic pancreatitis offers a sensitivity of 60% and a specificity of 83% to diagnose chronic pancreatitis with a high positive predictive value, an excellent correlation with ERCP for moderate and severe chronic pancreatitis ($\kappa = 0.82$) and a good interobserver correlation ($\kappa = 0.45$)[31,32]. On the other hand, the presence of less than 3 endosonographic criteria has a high negative predictive value for chronic pancreatitis (85%)[31].

EUS has also proved its value to diagnose biliary and pancreatic tumours with a diagnostic accuracy higher than CT especially in those tumours smaller than 2.5 cm in diameter[33,34] with a negative predictive value close to 100%[35]. Furthermore, in these cases EUS allows a correct staging with a resectability accuracy of 67%[36] and the ability to obtain a cytological diagnosis with a sensitivity of around 89%, a specificity of 99% and a diagnostic accuracy of 96%[37].

EUS can also diagnose the presence of pancreatic cysts which might be responsible for the acute pancreatitis bout, especially those cysts communicated with the pancreatic duct such as Intraductal Papillary Mucinous Neoplasm (IPMN)[38]. This entity can cause recurrent pancreatitis, probably by means of intermittent pancreatic duct obstruction related to mucus plugs. EUS is fairly reliable in differentiating IPMN from chronic

pancreatitis[39]. Mucinous and serous cystic neoplasms rarely communicate with the pancreatic duct and therefore rarely cause pancreatitis. Thus, EUS can help to distinguish between serous and mucinous cystic neoplasms by the morphological aspects, although no endosonographic features have proved to be consistently reliable for distinguishing benign from malignant lesions[40]. Furthermore, EUS offers the possibility of performing FNA and analysing the cyst fluid with determination of tumor antigens, fluid viscosity, mucin staining, amylase concentration, analysis of genetic mutations associated with tumours and cytology. These determinations may improve diagnostic accuracy[41]. However, EUS findings by themselves are not accurate enough to definitively diagnose the nature of the pancreatic cystic lesion and cyst fluid cytological or laboratory analysis may not provide a reliable and definitive diagnosis which is sometimes impossible until surgical excision is done[42].

Besides the diagnostic accuracy, the possibility of performing sphincterotomy on EUS[43] has recently been described. This therapeutic role of EUS should be confirmed in the next few years.

MRCP is a non invasive exploration which has also proved its value in diagnosing entities responsible for an acute pancreatitis bout such as chronic pancreatitis, sphincter of Oddi dysfunction, anatomic anomalies and choledocolithiasis[44,45]. Studies testing the role of MRCP in the setting of IAP are scarce but it can be useful, especially when MRCP is combined with secretin test showing a positive predictive value for the diagnosis of sphincter of Oddi dysfunction of 100%, but with a disappointing negative predictive value of 64%[44]. However, to my knowledge, MRCP and EUS have never been prospectively compared in this setting.

The main support for performing EUS in patients with IAP is its high diagnostic accuracy especially in diagnosing the presence of microlithiasis[34] which is the most frequent finding. In these cases, performing a cholecystectomy reduces the recurrence of pancreatitis from 66%-75% in untreated patients to 10% in patients who undergo cholecystectomy[2,13,17]. EUS is a relatively invasive technique with a minimum but present risk of complications and it might be more uncomfortable for the patient. On the other hand, MRCP has not yet proved its value in patients with IAP although it can diagnose the majority of causes for pancreatitis except for microlithiasis.

Taking this background into account, in my opinion but not shared by other authors[46], it is out of discussion that the first diagnostic exploration for patients with IAP and gallbladder in situ is EUS. Debate must be open in patients already cholecystectomized, in whom chronic pancreatitis, sphincter of Oddi dysfunction and pancreas divisum are the most frequent etiological findings and MRCP has demonstrated good accuracy to diagnose these entities[45]. However, EUS has proved to be superior in detecting choledocholithiasis smaller than 5 mm[47,48]. Therefore, when choledocholithiasis is strongly suspected, a negative MRCP should be followed by EUS. So the decision to perform EUS or MRCP as the first choice diagnostic procedure in cholecystectomized pa tients must be made by taking into account other factors. These factors include local expertise and personal records of patients such as claustrophobia, gastric surgery etc. ERCP should remain as a therapeutic exploration when necessary[46].

Unfortunately, to my knowledge, there are still no prospective reports comparing the diagnostic accuracy of EUS with MRCP on patients with IAP. We are currently performing a prospective double blinded study comparing the diagnostic yield of EUS and MRCP in order to clarify their role in the diagnostic work up of patients with IAP.

DO WE HAVE TO STUDY EVERY PATIENT WITH IAP OR ONLY THOSE WITH A RECURRENT DISEASE?

There is some controversy in the literature about this subject. Some authors have questioned the efficacy of EUS in cases of relapsing pancreatitis[49]. This topic has been evaluated in previously published papers comparing the diagnostic yield of EUS in IAP patients with a single episode or a recurrent disease, proving that the diagnostic yield of EUS does not significantly change between both groups[23-25]. So, it seems that the diagnostic yield of EUS is similar both in patients with a single episode of pancreatitis and in patients with recurrent disease and is therefore useful in both situations. This opinion is shared by other authors[50,51].

WHAT IS THE BEST MOMENT TO PERFORM EUS?

The best moment to perform the EUS exploration in patients with IAP is another confusing and difficult question to answer and there are as many possibilities as published reports. Norton *et al*[20] perform EUS when patients resume food intake; Liu *et al*[22] perform EUS when the acute pancreatitis bout has resolved normally during admission; Tandon *et al*[23] when symptoms of acute pancreatitis have subsided, normally 2 or 3 wk after the acute phase; and Yusoff *et al*[25] perform the exploration at least 4 wk after the acute episode in order to assure that acute pancreatic parenchymal changes have resolved when EUS is performed.

In our endoscopy unit we agree with the latter author and perform EUS at least four weeks after hospital discharge in order to assure a complete resolution of the acute parenchymal alterations which would lead to misdiagnosis. Another reason to do so is to differentiate gallbladder microlithiasis related to acute pancreatitis fasting which would be a consequence of the disease from previously present microlithiasis which would be the cause of the disease. To perform EUS at least four weeks after

hospital discharge has two major disadvantages: firstly, an existing prepapillar choledocholithiasis might not be diagnosed with the potential of a re-bout. Secondly, since there is a potential risk of losing the patient for follow up after clinical improvement, a small pancreatic tumor might be missed.

In conclusion, EUS offers a high diagnostic yield in patients with IAP and should be considered the first diagnostic procedure to perform in these patients, even in those with a single episode. MRCP can also be valuable in this setting, but its role should be defined in prospective comparative studies, especially in cholecystectomized patients.

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