The role of endoscopic ultrasonography in the etiological evaluation of idiopathic acute pancreatitis

J. J. Vila, F. Borda and F. J. Jiménez

Gastroenterology Department. Hospital de Navarra. Pamplona, Spain

RESUMEN

Hasta el 30% de los pacientes con pancreatitis aguda son diagnosticados de una pancreatitis aguda idiopática tras un estudio inicial que debe incluir una anamnesis completa, exploración física, análisis con determinación de calcio y triglicéridos y al menos una ecografía abdominal. Esta situación representa un reto diagnóstico, aunque en la mayoría de los casos se encuentra una causa que justifique la pancreatitis tras realizar diferentes exploraciones diagnósticas. En los últimos años la ecoendoscopia está demostrando ser de gran utilidad en el estudio de estos pacientes, produciendo a cambio una baja morbilidad. En este artículo hacemos una revisión del papel de la ecoendoscopia en el estudio etiológico de la pancreatitis aguda idiopática.

Palabras clave: Ultrasonografía endoscópica. Pancreatitis. Etiología.

ABSTRACT

Up to 30% of patients with acute pancreatitis are diagnosed of idiopathic acute pancreatitis after an initial evaluation including a complete clinical history, physical examination, analysis with calcium and triglycerides determination, and at least one transabdominal ultrasonography. Unexplained pancreatitis represents a diagnostic challenge, although after different explorations a cause is found in the majority of these patients. During the last years endosonography has proved to be a low morbidity exploration very useful in the evaluation of patients with this entity. In this article we review the role of endosonography in the etiologic study of patients with idiopathic acute pancreatitis.

Key words: Endosonography. Pancreatitis. Etiology.

INTRODUCTION

A cause is found in 70-90% of cases during the initial study of acute pancreatitis. This initial study should include: A detailed medical history including recent infection, abdominal trauma or surgery; alcohol and drug use, and systemic diseases. The following should also be assessed: Family history of pancreas disease; blood tests with serum calcium and triglycerides, and at least one abdominal ultrasonogram to rule out lithiasis in the bile tree. In our department we obtain at least two abdominal ultrasonograms when the first one fails to identify bile lithiasis. If following this initial study no cause of pancreatitis is found, we call it idiopathic acute pancreatitis (IAP), which is the third most common etiological group in most series after biliary and alcoholic pancreatitis (1,2).

However, whether we eventually diagnose a cause for pancreatitis in patients with IAP will depend on the extent of our diagnostic work-up. By performing selected exams such as microscopic bile examination (MBE), echoendoscopy (EUS), magnetic resonance cholangiography (MRC), or endoscopic retrograde cholangio-pancreatography (ERCP) we may diagnose a cause for pancreatitis in up to 90% of IAP cases.

The strategy used in our department for IAP includes EUS as the initial examination. We based our decision on the diagnostic yield shown by EUS for these patients in a number of studies (3-5), as well as its low complication rate despite being an invasive technique.
The goal of this paper is to review the role of EUS in the study of patients with IAP considering the various etiologies involved. We shall previously discuss the causes potentially involved in IAP as revealed by in-depth etiological studies. On the other hand we assess the information available in the literature on the influence of selected IAP patient conditions in the diagnostic performance of EUS.

**CAUSES OF IAP**

It is important that the cause of IAP be identified, as failing to act upon it may favor pancreatitis relapse. Relapse rate oscillates between 4 and 70% according to the actual cause of pancreatitis (6-8). Thus, when the cause of pancreatitis is bile mud or micro lithiasis, and no therapy is administered, relapse rates have been seen to oscillate between 30 and 70% during 2 to 3 years’ follow-up (9,10). Other authors have described a relapse rate of up to 50% within one year, this relapse rate increasing with follow-up duration (11,12). In addition, overall mortality rates for pancreatitis range from 4 to 9%, and such rates may be even higher for idiopathic acute pancreatitis (13).

The most frequent cause of IAP in patients with an *in situ* gallbladder is bile micro lithiasis, which accounts for up to 80% of cases (9,14,15). The gold standard for the diagnosis of micro lithiasis still is microscopic bile examination (MBE) (16,17), with sensitivity ranging from 65 to 90%, and specificity from 88 to 100% (18). However, this technique has limitations. Between 29 and 50% of patients with known bladder lithiasis have a negative MBE (3,19). In our experience MBE is a time-consuming technique that not rarely will take up 1 hour; also, it cannot be performed in 20% of cases due to patient intolerance, failed duodenal probing, or wrong material aspiration. This rate according to our experience is consistent with that seen by other teams in our setting (20).

Once micro lithiasis is demonstrated patients must undergo cholecystectomy (9,14). It has been demonstrated that thus the recurrence rate for pancreatitis is reduced to around 66-75% in untreated patients, and less than 10% in patients receiving cholecystectomy (9,14,20). In case of excessive surgical risk an endoscopic therapy using sphincterotomy, or a medical regimen using ursodeoxycholic acid may be attempted (6,14).

The second most common abnormality we may find in these patients is sphincter of Oddi dysfunction. It may account for up to 30% of IAP cases, and is a most common diagnosis in cholecystectomized patients with IAP (3,4,6,15,21-23). To confirm this, a manometry of the sphincter of Oddi may be performed, particularly in patients with suspected sphincter of Oddi dysfunction, types II and III (23). Sphincter of Oddi manometry is a technique available in few sites, which may induce acute pancreatitis in 17 to 33% of patients (24-27), and must thus be carried out by reference units (28). The treatment of choice for patients with sphincter of Oddi dysfunction is endoscopic sphincterotomy, but we may see relapsing pancreatitis in up to 25% of patients (21). In that case, a sphincterotomy at the pancreatic sphincter is recommended (21,23).

Other causes of pancreatitis that we may find on gaining insight into the study of these patients include anatomical abnormalities. *Pancreas divisum* is most common. However, while the presence of *pancreas divisum* has been described in up to 26% of patients with IAP, there is still debate on whether this abnormality may be eventually considered a cause of IAP, as it is highly prevalent in the general population (15,29,30). It is accepted as a potential cause of IAP when the presence of minor papillary stenosis is revealed using Warshaw’s test (6). Treatment consists of endoscopic sphincterotomy on the minor papilla (21,31).

Another abnormality that we may find is a much too long common Wirsung and bile duct, more than 15 mm in length (32). This must also be treated with endoscopic sphincterotomy (31).

Other anatomical abnormalities that may justify an acute pancreatitis episode include choledochoceles, Wirsung stenosis, annular pancreas, periam pillary diverticulum, and duodenal duplication cyst (3,4,6,15,23). Overall, anatomical abnormalities may account for up to 20% of IAP cases (15).

Between 5 and 7% of IAP cases result from a biliary-pancreatic tumor (3,23). An association between age and incidence of these tumors has been described; a study reported as an abstract only describes an incidence of bilipancreatic tumors of 3% in patients younger than 40 years with IAP, of 21% for those between 40 and 60 years of age, and of 25% in subjects older than 60 (33). This means that we should consider this cause particularly for patients with IAP who are older than 40 years, as other authors also point out (3,34).

Chronic pancreatitis is also considered a potential cause of IAP when previously unknown. A diagnosis of this illness may be reached using various techniques such as exocrine pancreatic function tests, abdominal CT, ERCP, EUS, or MRC, and often combining a number of these modalities (35). Chronic pancreatitis may be both a cause and a consequence of IAP, this being a challenging clinical dilemma that may occur in these patients (6,23,24,36). Anyway, it is important that chronic pancreatitis is diagnosed when present, as this will have a significant impact on patient management (23).

Autoimmune pancreatitis has been an increasingly significant condition as a cause of IAP in recent years. Measuring antinuclear and IgG4 antibodies is useful in the diagnosis of this condition (37).

When all the above causes have been examined it is advisable that we consider alcoholic pancreatitis anew, since patients are not uncommonly reluctant to report their drinking given this habit’s negative connotations.
If none of the above-mentioned causes of IAP is eventually diagnosed, pancreatitis of genetic origin is considered most likely—mutations in genes coding for cationic trypsinogen (PRSS1), protease inhibitor Kazal type I (SPINK-1), cystic fibrosis transmembrane conductance receptor (CFTR), and α1-antitrypsin deficiency. Researching these mutations may be an option particularly when dealing with younger patients, but its use in daily practice is not recommended because of the nil therapeutic implications a positive result may have (3,22,23). Overall, genetic causes are thought to account for up to 5% of IAP episodes (15).

If the latter causes are also not demonstrated, the condition is considered a true idiopathic pancreatitis condition.

ENDOSCOPIC ULTRASONOGRAPHY IN IDIOPATHIC ACUTE Pancreatitis

A glimpse at the aforementioned causes of IAP will show that, at least theoretically, most of them may be ultimately diagnosed with EUS. In fact, its theoretical diagnostic yield is very similar to that of ERCP, except that it cannot diagnose sphincter of Oddi dysfunction (38).

EUS reveals lithiasis as arch-like hyperechogenic images with a posterior shadow in the gallbladder or common bile duct. Bile mud is translated as the presence of hyperechogenic sediment. Microlithiasis is seen as point-like echoes with mid to high echogenicity that fleetingly develop within the bladder (Fig. 1).

On the other hand, EUS is presently considered a most sensitive technique in the diagnosis of chronic pancreatitis (39,40). A number of parenchymal and ductal criteria is available (Table I). The presence of 3 such criteria is deemed to suggest chronic pancreatitis (39). To increase specificity the presence of at least 5 of such criteria offers a sensitivity around 60%, and a specificity of 83% with a high positive predictive value, excellent correlation to ERCP for moderate to severe chronic pancreatitis (κ = 0.82), and good inter-observer consistency (κ = 0.45) (41-43). When fewer than 3 diagnostic criteria are present chronic pancreatitis is very unlikely (NPV > 85%) (41). EUS also allows a quantitative analysis of the pancreatic parenchyma, which may increase sensitivity regarding the diagnosis of early chronic pancreatitis (39,44).

EUS is also a highly sensitive technique to detect pancreas tumors, particularly in patients with tumors smaller than 2.5 cm in diameter, with a diagnostic accuracy that is significantly higher than that of CT (45,46), and a negative predictive value neighboring 100% (47). Furthermore, in such cases EUS allows appropriate staging with 67% diagnostic accuracy for resectability (48), and a cytological diagnosis with a sensitivity around 89%, specificity at 99%, and diagnostic accuracy of 96% (49) (Fig. 2).

The diagnosis of pancreas divisum is surely the most challenging one from a technical viewpoint, and requires ample experience. A number of ultrasonographic signs have been described for this diagnosis. One is an absent “stack sign”, that is, the common bile duct and Wirsung duct as seen in a longitudinal duodenal slice approaching the papilla. This sign occurs in 33% of patients with pancreas divisum versus 83% of patients without this anatomical abnormality (p = 0.04) (50). Another reported sign that seems more specific is the presence of Santorini’s duct to the duodenal wall (51,52) (Fig. 3). When identified, the presence of a ventral-to-dorsal pancreatic duct must be excluded. EUS has a high negative predictive value when a branch fusion between the ventral and dorsal pancreatic ducts is revealed (52). The diagnosis of pancreas divisum seems more straightforward using a sectorial endoscope, regarding which a diagnostic accuracy of 97% has been reported (53).

<table>
<thead>
<tr>
<th>Table I. Endosonographic criteria for chronic pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal</td>
</tr>
<tr>
<td>Heterogeneous sonographic pattern</td>
</tr>
<tr>
<td>Hypoechoic foci (1-3 mm)</td>
</tr>
<tr>
<td>Echogenic foci</td>
</tr>
<tr>
<td>Prominent interlobar septa</td>
</tr>
<tr>
<td>Lobular pancreatic margin</td>
</tr>
<tr>
<td>Hypoechoic areas (&gt; 5 mm)</td>
</tr>
<tr>
<td>Pancreatic calcifications</td>
</tr>
<tr>
<td>Ductal</td>
</tr>
<tr>
<td>Duct caliber &gt; 3 mm</td>
</tr>
<tr>
<td>Tortuous pancreatic duct</td>
</tr>
<tr>
<td>Intraductal echogenic foci</td>
</tr>
<tr>
<td>Hyperechogenic duct wall</td>
</tr>
<tr>
<td>Secondary branch ectasia</td>
</tr>
</tbody>
</table>

Fig. 1. A patient with a recent history of idiopathic acute pancreatitis in whom EUS reveals several hyperechogenic points corresponding to microlithiasis (arrows).
On the other hand, an acceptable correlation between EUS-guided Warshaw’s test and sphincter of Oddi manometry in the diagnosis of sphincter of Oddi dysfunction ($\kappa = 0.53$), with both a positive and negative predictive value of 80%, but a low sensitivity at only 57% (54). However, similar results have not been reported by other authors.

In the last few years several papers assessing the diagnostic yield of EUS in subjects with IAP as primary or secondary endpoint have been reported (51,52,55-61). While some papers with a higher level of scientific evidence have been published (57,61), most of these studies may be categorized as scientific evidence level IV and recommendation grade C (62). EUS diagnostic yield as reported in these papers ranges from 60 to 80%, but some considerations should be borne in mind when evaluating their results.

The first study reported was the one by Dahan et al. (61), with the goal of comparing EUS diagnostic accuracy to MBE for the diagnosis of microlithiasis in patients with biliary colic or IAP. They included 45 patients and obtained a diagnostic accuracy that was significantly higher with EUS. However, no newer papers have been published where similar results were obtained.

Norton et al. (55) assessed EUS diagnostic yield in 44 patients with IAP for the diagnosis of previously unknown lithiasis, and compared this to a control group with 25 patients. They found biliopancreatic disorders in 32 patients (72%), and bile lithiasis was the most common finding, seen in 26 patients (59%) but with two false positive choledocholithiasis results.

Then Frossard et al. (56) assessed the usefulness of EUS in diagnosing biliary disease or chronic pancreatitis in 168 patients with IAP, and had as gold standard surgery results in 101 cases, ERCP in 49, and MBE or evolutionary clinical monitoring in the remaining 18 patients. In 135 of these patients (80%) EUS found an abnormality, which was biliary in 124. On comparing results to those of their gold standard, the diagnosis reached with EUS was seen to be right in 92% of patients.

In a later study Liu et al. (57) evaluated the usefulness of EUS in identifying the presence of cholelithiasis and other potential etiologies in 18 patients with IAP. They found bladder lithiasis in 14, and 3 of them had concomitant choledocholithiasis, which was all confirmed by surgery or ERCP.

Tandon et al. (51) used EUS to examine 31 patients with IAP, and found a potential cause in 21 (78%): Microlithiasis in 5, chronic pancreatitis in 14, pancreas divisum in 2 (one of them with concomitant chronic pancreatitis), and a pancreas tumor in 1. In assessing this study’s results the fact that patients with moderate or even high alcohol intake were not excluded should be borne in mind. In fact, of all 14 with chronic pancreatitis, 10 had recognized moderate to severe alcohol use. Therefore, these patients may have had no IAP but bouts of alcohol-related chronic pancreatitis exacerbation. Also, the fact that these patients with likely alcoholic pancreatitis were enrolled increases pre-test probabilities that chronic pancreatitis parameters are found (38). This, and the fact that they consider the presence of three signs on EUS a diagnosis with chronic pancreatitis, accounts for the high percentage of patients with this disease in their series (45%).

Coyle et al. (58) measured the diagnostic yield of ERCP plus MBE and/or sphincter of Oddi manometry versus EUS in patients with IAP. To that end they enrolled 90 patients —88 underwent ERCP, 67 sphincter of Oddi manometry, and 56 EUS. By combining these techniques they diagnosed sphincter of Oddi dysfunction in
28 patients (31%), bile lithiasis in 18 (20%), chronic pancreatitis in 18 (20%), *pancreas divisum* in 18 (20%), and pancreas tumors in 8 patients (8.9%). They found no cause in 18 patients (20%).

Both Tandon et al. and Coyle et al. consider that three ultrasonographic criteria suffice for the diagnosis of chronic pancreatitis. In our unit we require the presence of at least 5 chronic pancreatitis criteria, an aspect on which we agree with other authors (38,52). This decreases sensitivity but increases specificity and PPV (41-43,63).

The most comprehensive study to date is the one by Yussoff et al. (52). Their series included the EUS results from 370 patients with IAP. In patients with in situ gall-bladder and normal EUS bile was aspirated for MBE. Excluding chronic pancreatitis, they found a cause of IAP with EUS in 108 patients (29.2%): Any form of bile lithiasis in 50 patients (13%), pancreas divisum in 27 (7.3%), intraductal mucinous tumor or other cystic tumor in 10 patients (2.7%), solid pancreatic tumor in 3 (0.8%), and other causes in 18 patients (4.8%). On the other hand, 109 patients (29.4%) met chronic pancreatitis EUS criteria, and thus EUS yield rises up to 58.6% when this cause of IAP is included, which is more consistent with other reported papers. Chronic pancreatitis was thus the most commonly encountered cause in patients both with and without their gallbladder, and significantly more common in patients with recurring IAP. In this study the one factor that was associated with positive EUS findings was age—the older the age group, the higher the odds that a cause of IAP was found by EUS.

This study is unclear on whether ultrasonographic micro-lithiasis signs are considered a positive finding, as only the presence of choledolithiasis or choledocholithiasis and bile mud seem to be taken into account. Micro-lithiasis is certainly considered a cause of IAP, and 80 patients with in situ bladder and a normal EUS undergo MBE, which reveals microcrystals in 38. While MBE is still considered the technique of choice in the diagnosis of micro-lithiasis (16,17), previous studies showed that EUS was superior to MBE for the identification of bladder micro-lithiasis (61). On the other hand, the high percentage of patients with chronic pancreatitis signs also stands out. This may result from the fact that this study included no patient with severe drinking in the two weeks leading to the IAP episode, and hence such patients with secondary chronic pancreatitis may have been included.

In the latest study reported Garg et al. performed ERCP, MBE, and EUS procedures on 75 patients with IAP, and found a potential cause in 57 patients (76%), with chronic pancreatitis and micro-lithiasis being most common (60). In addition to adult patients, EUS has also proven useful in pediatric subjects with IAP (59).

Despite the fact that all these studies show the high diagnostic yield of EUS in patients with IAP, patient follow-up is only included in two (51,57). The study by Liu et al. (57) had a mean follow-up of 20 months during which no new diagnoses of choledolithiasis were made in patients where EUS had detected no bladder lithiasis. Tandon et al. (51) followed their subjects for an average of 16 months (range: 4-44 months), and the etiologic diagnosis provided by EUS was maintained in 87% of cases.

It then seems—according to these two studies—that EUS not only demonstrates the presence of potential IAP etiologies, but its results are consistent and remain valid over time in most patients, even though further studies are required to more appropriately evaluate this aspect (52).

### ADDITIONAL CONSIDERATIONS

Using EUS, and bearing in mind the results from studies reported in the literature, we may ultimately find the cause of IAP in a percentage ranging from 60 to 80% of patients. However, we must make some additional considerations on selected occasions. There is debate on whether EUS diagnostic yield warrants its use after recurring or initial IAP; on whether it should be used in both patients with in situ gallbladder and cholecystectomized subjects; or on what is the best timing for EUS after acute disease.

Regarding the appropriateness of EUS after a first IAP episode or only after recurring IAP there is controversy in the literature, with authors that question the usefulness of EUS in patients with recurring IAP (38). However, in published studies no significant differences are documented in EUS yield as regards patients with recurring IAP versus those who only suffered from one episode (51,52,58). In the study by Coyle et al. (58) the diagnostic yield of EUS is similar in all 24 patients with an initial episode of IAP and all 66 patients with recurring IAP, with a trend towards a higher proportion of pancreatic tumors in the recurring IAP group, with no significant difference however. In the paper reported by Yussoff et al. (52) a primary goal was to ascertain whether EUS yield is similar in both groups of patients. Among all 246 patients with in situ gallbladder EUS identified a cause in 31.3% of patients with an initial IAP episode, and 32.1% of those with recurring IAP (p = 0.89). When chronic pancreatitis was included as a cause of IAP, EUS showed a significantly higher yield in patients with recurring disease: 53 vs. 74.1%, respectively (p = 0.0009). No differences in EUS yield were found among cholecystectomized patients according to the initial or recurring nature of their pancreatitis episode, both when chronic pancreatitis was included (46.3 vs. 56.1%; p = 0.28) and excluded (29.9 vs. 17.5%; p = 0.14).

In the face of these data we may state that EUS diagnostic yield is similar after an initial episode and a recurring episode of IAP, and that EUS is consequently useful in both conditions. This view is shared by other authors (64).
Another aspect to consider in a patient with IAP is whether he or she has been cholecystectomized. Indeed, this has not been appropriately evaluated in published studies given the small number of cholecystectomized patients enrolled (51,55,57). In other papers this factor is not taken into account during result assessment and categorization (56,58). A study that does classify EUS results according to gallbladder status is the one by Yusoff et al. (52). This series includes 246 patients with in situ gallbladder, and 124 cholecystectomized subjects. With EUS they found a cause in 31.7 and 24.2% of patients, respectively. When chronic pancreatitis is included as a potential etiology these percentages rise up to 62.6 and 50.8%, respectively. We may see that this percentage is always higher for patients with an in situ gallbladder. This relates to the EUS-mediated diagnosis of bile lithiasis, either as choledolithiasis, bile mud, or microlithiasis. As previously mentioned, up to 80% of patients with IAP have microlithiasis in some studies (4,9,15).

Since the most commonly cause of IAP in cholecystectomized patients includes chronic pancreatitis and anatomical variants, MRC should be suggested as their initial exam. This is a non-invasive exploration that also permits a highly accurate diagnosis of these conditions (56,65-67). While no studies compared MRC and EUS in terms of diagnostic yield in patients with IAP, EUS did show better results in the diagnosis of small-sized choledocolithiasis (68,69), a commonly found cause in these subjects (Fig. 4). With this and the better availability of EUS in our department in mind, we prefer EUS as the initial exploration in the etiologic study of these patients. Anyway, no data in the literature conclusively support any of these techniques, and their choice is surely a decision individualized for each patient and center (69).

EUS proper timing after an IAP episode is also unclear and varies from one author to the next. Norton performs EUS when patients eat normally (55); Liu uses it when the acute pancreatitis episode is over, and performs most exams while the patient is still in hospital (57); Tandon performs EUS when pancreatitis symptoms have subsided, most often at 2-3 weeks after discharge (51); Yusoff performs EUS at least 4 weeks after the last IAP episode, in an attempt to ensure that parenchymal changes will correspond to chronic pancreatitis rather than residual inflammation (52).

We agree with the latter author, and rather order EUS at least 4 weeks after discharge. We do so to avoid identifying bile microlithiasis secondary to bile stasis resulting from patient fasting during acute pancreatitis as a cause. On the other hand, we seek the elimination of residual inflammation sites after acute pancreatitis.

CONCLUSIONS

To conclude we may say that EUS is a technique offering a high diagnostic yield in patients with IAP, which can diagnose the cause of pancreatitis in up to 80% of patients. This performance is similar in patients with only one episode of IAP, patients with recurring IAP, patients with in situ gallbladder, and cholecystectomized patients. It would be highly advisable that prospective, controlled studies be carried out to compare the usefulness of EUS versus MRC in these patients.

Despite the fact that studies reporting on this subject are few and have a moderate scientific evidence level, given the aforementioned diagnostic yield of EUS and its low complication rate, similar to that of gastroscopy (70,71), our department uses EUS as the initial exploration for patients with IAP. We do this even after initial episodes, particularly in patients with in situ gallbladder, but also in cholecystectomized subjects, at least after four weeks following hospital discharge.

REFERENCES


