Utility of endoscopic ultrasound in idiopathic acute recurrent pancreatitis

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ABSTRACT:
Idiopathic acute recurrent pancreatitis (IARP) is defined as at least two episodes of acute pancreatitis with the complete or near-complete resolution of symptoms and signs of pancreatitis between episodes, without an identified cause. There is a paucity of information about the usefulness of endoscopic ultrasound (EUS) in IARP.

Objectives To determine the diagnostic yield of EUS in IARP.

Design A retrospective study was performed in patients with IARP evaluated by EUS between January 2009 and December 2016. Follow-up assessments of acute pancreatitis recurrence were carried out.

Results Seventy-three patients with 102 EUS procedures were included. EUS was able to identify the cause of IARP in 55 patients (75.3%). The most common findings were chronic pancreatitis in 27 patients (49.1%), followed by biliary lithiasis pathology in 24 patients (43.6%), and intraductal papillary mucinous neoplasm in four patients (7.3%). A directed treatment against EUS findings had a protective tendency associated with the final resolution of recurrence. There were no complications reported.

Conclusion EUS performed in patients with IARP helped to identify a possible cause in 2/3 of the cases. The majority of patients have a treatable disease.

INTRODUCTION
Acute pancreatitis (AP) is the most common disease affecting the pancreas and has a high incidence worldwide.1 After the first attack of AP, 22% develop at least one episode of recurrence and 10% develop chronic pancreatitis (CP).1,2 Risk factors for the transition to recurrent and CP is related to the cause of AP.3 However, the cause is not always obvious, despite the complete evaluation of history, laboratory and imaging. Approximately 10%–30% of patients with AP are in a category labelled as idiopathic AP (IAP).2,4–7 This group is prone to a high recurrence rate that can reach up to 70%.8 Acute recurrent pancreatitis is defined as at least two episodes of AP with the complete or near-complete resolution of symptoms and signs of pancreatitis between episodes.2,6 In this scenario, a more extensive assessment including endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) is used to determine the aetiology.7

EUS has been reported to be the imaging of choice for the pancreas and biliary tract. EUS is a safe, minimally invasive diagnostic procedure in patients with idiopathic acute recurrent pancreatitis (IARP). The diagnostic yield of EUS might be up to 80% of patients.8,9 The aim of this study was to evaluate the diagnostic yield of EUS in patients with IARP.

METHODS
A retrospective study based on a prospective data collection was conducted at a single tertiary institution from January 2009 to December 2016. The information was obtained from endoscopic reports as well as
physical and electronic health records from patients diagnosed with IARP. All patients underwent EUS examination. Exclusion criteria included the following: patients aged under 15 years; medical contraindication for EUS; patients referred from another institution; a documented ongoing alcohol and tobacco consumption; and metabolic conditions known to predispose to pancreatitis (including hyperparathyroidism, hypercalcaemia and hypertriglyceridaemia of more than 500 mg/dL).

In our centre, all patients with pancreatic diseases are evaluated, followed and treated by the Pancreas Clinic, as formed by gastroenterologists, pancreatologists, endoscopists and surgeons with a special interest in pancreatic diseases. Demographic data (age, sex, weight and height), prior surgery, previous AP and comorbidity were collected. Preprocedural laboratory tests were run on the entire cohort in order to assess the security of the procedure and the risk of bleeding. Diagnostic indications and the results of imaging techniques and EUS data were obtained.

EUS examinations were performed by two endoscopic sonologists with experience of more than 3000 EUS procedures. All patients underwent standard monitoring with a continuous display of the heart rate and pulse oximetry along with blood pressure. EUS procedures were performed under conscious sedation provided by an anaesthesiologist assisted by trained nurses. A linear echoendoscope GF-UCT140 (Olympus, Tokyo, Japan) with an Aloka ultrasound machine SSD-5500 (Aloka, Tokyo, Japan) and a linear echoendoscope FUJI (eg, -530UT) with an ultrasound machine SU-8000 ( Fuji-film, Minato-Ku, Tokyo, Japan) were used. Patients were hospitalised and underwent strict supervision for at least 2 hours after the procedure. Informed consent was obtained from all patients prior to the endoscopic procedure.

Definitions

The Atlanta classification 2012 was used to define AP: The diagnosis requires two of the following three features: (1) abdominal pain consistent with AP; (2) serum lipase or amylase activity at least three times greater than the upper limit of normal and (3) characteristic findings of AP on imaging (contrast-enhanced CT (CECT), MRI or transabdominal ultrasonography). IARP is defined as a condition in which at least two well-documented episodes of AP have occurred, with the resolution of symptoms between each episode. It is characterised by an absence of morphological criteria for CP by MRI or CECT and the absence of a specific diagnosis following clinical history and physical examination; laboratory data including triglyceride and calcium concentrations; a review of all medications, both prescription and over-the-counter and cross-sectional abdominal imaging studies including abdominal ultrasound for all patients with a gallbladder in situ. Severity was defined by the Atlanta classification 2012. We considered EUS findings to be diagnostic if they could explain RAP. Biliary aetiology was considered as follows: microlithiasis was defined as a hyperechoic signal of 0.5–3 mm without a postacoustic shadow. Biliary sludge was defined as moving echoes of low amplitude in the lumen of the gallbladder without any postacoustic shadow. Gallstones were defined as moving echoes of high amplitude of more than 3 mm, with a postacoustic shadow. These findings could be present inside the gallbladder or common bile duct. CP was diagnosed according to the conventional criteria if five or more criteria were found; all identified endosonographic features were recorded. Pancreas divisum (PD) was diagnosed by EUS when there was clear evidence of a dominant dorsal duct with no evidence of communication between the ventral and dorsal ducts, with the ventral pancreatic duct coursing to the duodenal wall proximal and anterior to the bile duct, in the expected location of the minor papilla, or if the main pancreatic duct could not be traced from the major papilla. The diagnosis of autoimmune pancreatitis was established based on International Consensus Diagnostic Criteria.

After the EUS procedure, patients were followed up with clinical evaluation and recording of the presence of new episodes of AP. The last outpatient visit or inpatient stay was considered in the follow-up visitation.

Statistical methods

Demographic and clinical data were analysed using descriptive statistics, including absolute and relative frequencies. Median and minimum–maximum ranges were used in the nonparametric statistical analysis. We evaluated the association of the non-development of a new event of AP after treatment using the ORs. We calculated the OR as the likelihood that a new event of AP would occur given that the patient was undergoing treatment, compared with the odds of the outcome occurring in the absence of treatment. All analyses were performed using SPSS V.20.

RESULTS

Initially, the clinical records of a total of 101 patients were evaluated; 28 patients were excluded (figure 1). Seventy-three patients were included. In 55 (75.3%) patients, EUS findings were considered as diagnostic and in 18 (24.7%), they were non-diagnostic. Thirty-seven (67.3%) patients were male. The median age of the patients was 31 (range 15–75) years. The median of documented attacks of AP have occurred, with the resolution of symptoms between each episode. It is characterised by an absence of morphological criteria for CP by MRI or CECT and the absence of a specific diagnosis following clinical history and physical examination; laboratory data including triglyceride and calcium concentrations; a review of all medications, both prescription and over-the-counter and cross-sectional abdominal imaging studies including abdominal ultrasound for all patients with a gallbladder in situ. Severity was defined by the Atlanta classification 2012. We considered EUS findings to be diagnostic if they could explain RAP. Biliary aetiology was considered as follows: microlithiasis was defined as a hyperechoic signal of 0.5–3 mm without a postacoustic shadow. Biliary sludge was defined as moving echoes of low amplitude in the lumen of the gallbladder without any postacoustic shadow. Gallstones were defined as moving echoes of high amplitude of more than 3 mm, with a postacoustic shadow. These findings could be present inside the gallbladder or common bile duct. CP was diagnosed according to the conventional criteria if five or more criteria were found; all identified endosonographic features were recorded. Pancreas divisum (PD) was diagnosed by EUS when there was clear evidence of a dominant dorsal duct with no evidence of communication between the ventral and dorsal ducts, with the ventral pancreatic duct coursing to the duodenal wall proximal and anterior to the bile duct, in the expected location of the minor papilla, or if the main pancreatic duct could not be traced from the major papilla. The diagnosis of autoimmune pancreatitis was established based on International Consensus Diagnostic Criteria.

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Table 1  Aetiologies of acute pancreatitis documented by EUS in included patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n=55</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pancreatitis</td>
<td>27</td>
<td>49.1</td>
</tr>
<tr>
<td>Lithiasis pathologies</td>
<td>24</td>
<td>43.6</td>
</tr>
<tr>
<td>Gallbladder stones/sludge/microliathesis</td>
<td>2/16</td>
<td>–</td>
</tr>
<tr>
<td>Choledochal lithiasis/sludge/microliathesis</td>
<td>4/1/1</td>
<td>–</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>4</td>
<td>7.3</td>
</tr>
<tr>
<td>Main duct</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Branch-duct</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Mixed type</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

EUS, endoscopic ultrasound.

Table 2  Recurrence rate of pancreatitis in patients with treatable diseases detected by EUS classified by following treatment and without treatment according to EUS findings

<table>
<thead>
<tr>
<th>Patients with EUS attributed cause, n=28</th>
<th>With recurrence</th>
<th>Without recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>With treatment</td>
<td>24 (85.7)</td>
<td>21 (87.5)</td>
</tr>
<tr>
<td>With treatment and recurrence</td>
<td>3 (12.5)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Without treatment</td>
<td>4 (14.3)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

*Only patients with ‘treatable diseases’ detected by EUS are included in this table: lithiasis pathologies and intraductal papillary mucinous neoplasm.

EUS, endoscopic ultrasound.

Figure 1  Flow chart of the patients included. EUS, endoscopic ultrasound.

One hundred and two EUS examinations were performed in 73 patients. Twenty-two patients had two or more EUS (median 2, range 2–4). Seventeen were performed as part of a research protocol about the follow-up of ‘early CP’; in three patients requiring pancreatic pseudocyst drainage, one was evaluated prior and during a live demo, and one patient required the drainage of a 2 cm hepatic abscess in the left hepatic lobe.

Follow-Up data

The median follow-up was 36 months (range 1–144 months) after EUS. The incidence of new episodes of AP was lower for patients who underwent treatment according to EUS findings (table 2). Focused treatment according to EUS findings had a tendency towards the decreased risk of further episodes of AP, OR 0.14 (95% CI 0.01 to 1.43), with the number needed to treat (NNT) being 2.7 patients.

No complications associated with the EUS procedure were reported.

DISCUSSION

According to our data, EUS is a useful tool with high diagnostic accuracy in evaluating patients with IARP and the EUS-based management strategy appears to be associated with decreased recurrence rates. The initial evaluation failed to detect the cause in up to 30% of patients with acute recurrent pancreatitis. The EUS has been effective in providing useful information in such patients, including the identification of coeliacithiasis, microliathiasis and choledocholithiasis. This strategy might be used when other non-invasive modalities have failed to identify the aetiology, in addition to being a minimally invasive modality with high accuracy. However, there is a paucity of studies establishing the specific role of EUS in IARP.

In this study, the diagnostic yield of EUS in the current population was 75%, which correlates with previous publications reporting diagnostic yields varying from 29% to 88%. In a recent meta-analysis by Uman et al, the overall diagnostic yield was 59%, and the diagnostic yield of EUS was similar in the first episode compared to subsequent episodes.
with IARP (56% vs 52%). Biliary tract disease was the most common treatable aetiology, which is similar to that reported in other studies. In a prospective study including 31 patients, intraductal ultrasound detected the possible cause of IARP in 41.9% of patients. Bile duct stones and sludge were detected as the most common cause. Pereira et al reported a systematic review in patients with IAP undergoing EUS, in which biliary aetiology (microlithiasis or choledocholitiasis) was found in 37% of cases.

IARP is also defined as the occurrence of two or more episodes of AP without concurrent clinical or imaging evidence suggestive of CP by MRI, CECT or transabdominal ultrasonography. In our study, 27 (49.1%) patients were diagnosed with CP in spite of previous negative studies. It is well known that EUS can detect these kind of patients, which are sometimes considered negative studies. It is possible that the differences between the recurrence rates in these studies and our results are derived from differences in the aetiologies found in each group of patients. Also, we do not have access to a manometer in our centre to evaluate SOD. Therefore, we consider that the cause of the pancreatitis is directly related to the risk of recurrence.

Our study has some limitations. The first is the retrospective nature of the study, followed by the number of patients. However, the strength of our study is the close follow-up used to evaluate and demonstrate the performance of endoscopic and surgical treatment based on EUS findings. The strength of this approach was demonstrated by the tendency to avoid new AP episodes in most of patients, with a small NNT. Further limitations of our study include the fact that the present study is the fourth biggest sample reported in the majority of centres, including reference centres. In the most recent meta-analysis, they found high heterogeneity in diagnostic work-up before EUS. Finally, 102 EUS were performed in 73 patients; in four patients, the aetiology was found in the second procedure. Although EUS is a useful tool, as an operator-dependent tool and being subjective to interpretive error, the pathology could be overlooked. We have to mention that the data of the present study are important in the global data because our results exclusively include patients with IARP and all of these patients have undergone the EUS procedure; as a result, our paper is the fourth biggest sample reported to date.

In conclusion, EUS is a useful tool with high diagnostic accuracy in evaluating patients with IARP. An EUS-based management strategy appears to be associated with decreased recurrence rates.

Contributors Téllez-Ávila Fi, Tepox-Padrón A Bernal-Mendez RA, and Duarte-Medrano G designed the report; Téllez-Ávila Fi and Ramírez-Luna M performed endoscopic procedures; Tepox-Padrón A Bernal-Mendez RA, Duarte-Medrano G, and Marroquín-Reyes JD collected data; Téllez-Ávila Fi, Duarte-Medrano G, Bernal-Mendez RA, Romano-Munive AF, Mairena-Vallés M, Valdovinos-Andraca F, Uscanga L, Chan C, Domínguez-Rosado I, and Ramírez-Luna M organized the report; and Téllez-Ávila Fi, Tepox-Padrón A, Marroquín-Reyes JD, and Duarte-Medrano G, wrote the paper.

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Patient consent for publication Not required.
REFERENCES