

# Role of endoscopic ultrasound in idiopathic acute pancreatitis with negative ultrasound, computed tomography, and magnetic resonance cholangiopancreatography

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## Abstract

**Background** Idiopathic acute pancreatitis (IAP) is a diagnostic challenge. Finding a treatable cause after appropriate investigation may help to prevent recurrent pancreatitis and further management. The aim of our study was to retrospectively report our experience with endoscopic ultrasound (EUS) in investigating patients with IAP.

**Methods** Forty patients (26 males; age range: 17-72 years) of IAP with no underlying cause identified on transabdominal ultrasound, computed tomography and magnetic resonance cholangiopancreatography were studied. In 23 patients (57.5%), it was the first attack of acute pancreatitis whereas in 17 patients (42.5%) there was at least one previous attack of documented acute pancreatitis. EUS examination was done using a radial echoendoscope.

**Results** Twenty (50%) of the patients had biliary tract disease (cholelithiasis in 3, gallbladder sludge in 13, choledocholithiasis in 1 and common bile duct sludge in 3 patients). One each had an 8 mm tumor in the head of pancreas and pancreas divisum. No underlying cause could be found in 18 (45%) patients. Nine patients had features of chronic pancreatitis (CP) and the remaining had a normal pancreas.

**Conclusions** Occult biliary pathology is the predominant cause of IAP. Half of the cases without identified etiology already had an underlying CP. EUS is a very important tool in evaluating IAP especially after an initial negative diagnostic workup.

**Keywords** endoscopic ultrasound, pancreas divisum, cholelithiasis, chronic pancreatitis, endoscopic retrograde cholangiopancreatography

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## Introduction

Acute pancreatitis (AP) is a result of inflammation of pancreas without any previous morphological changes on imaging studies [1]. Alcohol and gallstone disease are the most common causes of AP. Other etiologies can be diagnosed with a detailed clinical and laboratory evaluation (including serum calcium, triglyceride, intact parathormone levels).

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Conflict of Interest: None

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Transabdominal ultrasound (US), contrast-enhanced computed tomography scan (CECT) of abdomen and magnetic resonance cholangiopancreatography (MRCP) are the routinely used imaging studies in the evaluation of severity and cause of AP. Despite a thorough diagnostic workup, in a variable proportion of patients (2-30%) a definitive cause cannot be established [2-5] and they are considered as idiopathic acute pancreatitis (IAP).

Endoscopic retrograde cholangiopancreatography (ERCP), endoscopic US (EUS), sphincter of Oddi manometry (SOM), bile microscopic examination (BME) and intraductal US (IDUS) are the armamentaria available for the evaluation of these patients. Depending on the availability and expertise, these tests are used alone or in various combinations at different centers in diagnosing IAP [5,6].

EUS is a minimally invasive modality used to investigate IAP. The ease to image the pancreas in close proximity to the probe, non-interference of the intestinal gases with image acquisition and availability of high frequency US probes makes EUS a very useful modality to investigate IAP. ERCP is

an invasive procedure involving cannulation of pancreatic or bile ducts with its antecedent complications (up to 5-10%) [7]. Given its high diagnostic accuracy and negligible complications (0.093% to 2.2%) [8], a EUS-based strategy may be a reasonable approach to evaluate patients with a single idiopathic attack. There is paucity of data on the utility of EUS in patients with IAP and many of these patients with inconclusive MRCP and computed tomography (CT) would either be offered empirical cholecystectomy or no treatment potentially leading on to repeated attacks of pancreatitis. In this study, we report our experience with EUS in investigating patients with AP with no history of alcohol consumption, normal biochemistry and negative US, CT and MRCP.

## Patients and Methods

A retrospective analysis of our database of the last three years of patients undergoing EUS for evaluation of IAP with no history of alcohol consumption, normal biochemistry and normal US, CT and MRCP was done. The diagnosis of AP was based upon compatible clinical history and examination with serum amylase levels at least 3 times the upper limit of normal. The patients included in the study denied a history of alcohol consumption and this was reconfirmed by interviewing the patients' relatives. As a part of etiological evaluation, these patients underwent serum biochemistry tests, abdominal US, abdominal CT, and MRCP. These patients did not have cholelithiasis or choledocholithiasis as documented by imaging modalities mentioned above, metabolic disorders including hypertriglyceridemia or hypercalcemia, history of surgery or abdominal trauma in the previous 3 months, consumption of toxic substances or medication that can cause AP, and family history of pancreatitis.

After obtaining an informed consent, EUS examination was performed using a radial echoendoscope (UTR 3830, Pentax Inc, Tokyo) at 7.5 MHz. The EUS examination was performed with the patient in a left-side recumbent position under conscious sedation with intravenous midazolam. The EUS examination was done at least 1 month after the attack of pancreatitis when the patients were pain free and were eating normally. Gallbladder sludge was diagnosed when echogenic material without acoustic shadows, which layered in the most dependent part of the gallbladder, was observed. The patients were diagnosed with chronic pancreatitis when at least 3 EUS criteria were observed. The included EUS criteria were: parenchyma changes (hyperechoic foci, accentuation of lobular pattern, small cysts, or focal regions of reduced echogenicity) and ductal changes (duct wall echogenicity, side-branch dilation, calculi, irregular pancreatic duct margins, and main duct dilation and narrowing) [9]. The patients with suspected diagnosis of chronic pancreatitis underwent a repeat EUS 4 to 6 months after the initial EUS to confirm the persistence of echo features.

The patients with choledocholithiasis diagnosed on EUS underwent ERCP and balloon sweep of the common bile duct after endoscopic biliary sphincterotomy. The diagnosis of choledocholithiasis was confirmed only if stones could be seen

endoscopically when extracted out of the ampulla following the balloon sweep. Similarly, the diagnosis of common bile duct sludge was confirmed if sludge or stone fragments could be seen endoscopically coming out of the ampulla following balloon sweep. Once cholelithiasis and/or biliary sludge were diagnosed by EUS, patients underwent elective cholecystectomy and the resected gallbladder was inspected to confirm the presence of stones and/or sludge. Histological examination of the gallbladder was also performed to confirm chronic cholecystitis and to exclude malignancy. The patients with confirmed chronic pancreatitis on second EUS were followed up and patients with persistent / recurrent abdominal pain with dilated main pancreatic duct underwent ERCP with stent placement with or without pancreatic sphincterotomy. Patients with small duct disease were treated medically. All the patients included in the study were followed up clinically every 3 months and further investigations were done depending on the disease evolution and diagnostic suspicion.

## Results

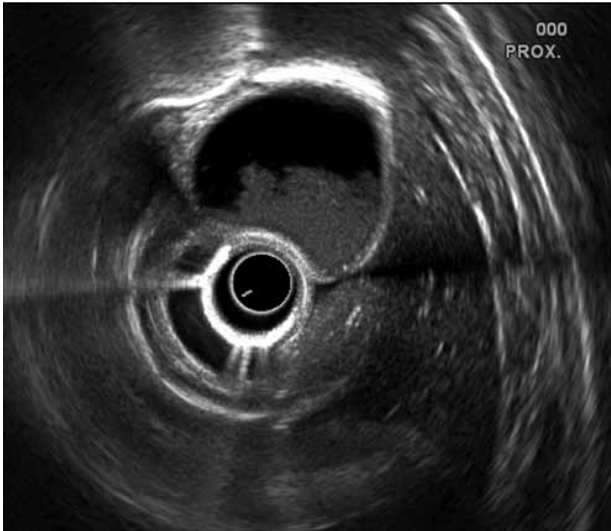
Over a three-year period, 40 patients (26 males; age range: 17-72 years) of IAP with no underlying cause found on transabdominal US, CT or MRCP were evaluated. In 23 patients (57.5%) it was the first attack of AP, whereas in 17 patients (42.5%) there was at least one previous attack of documented AP. All the patients underwent MRCP and US examination and CT was performed in 37/40 (92.5%) patients. None of the patients underwent ERCP prior to EUS.

20/40 (50%) of the patients had biliary tract disease on EUS (cholelithiasis in 3) (Fig. 1), gallbladder sludge in 13 (Fig. 2), choledocholithiasis in 1, and common bile duct sludge in 3 patients). One patient had an 8 mm tumor in the head of pancreas (Fig. 3). Pancreas divisum could be diagnosed in one patient. No underlying cause could be found on EUS in 18 (45%) patients.

Of these 18 patients, 9 patients had EUS features of chronic pancreatitis (Fig. 4) and on follow up they had recurrent



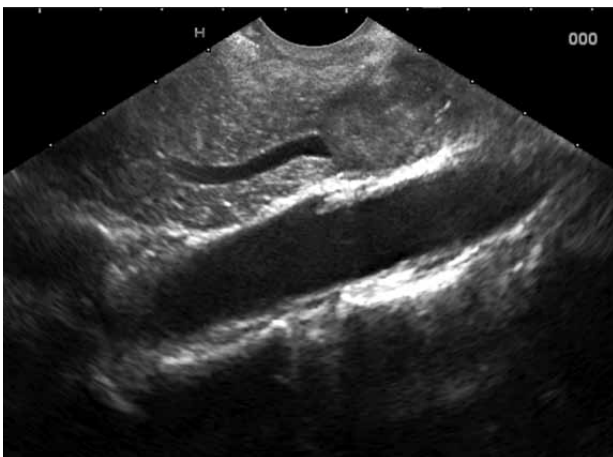
**Figure 1** Endoscopic ultrasound showing a small gallbladder calculus



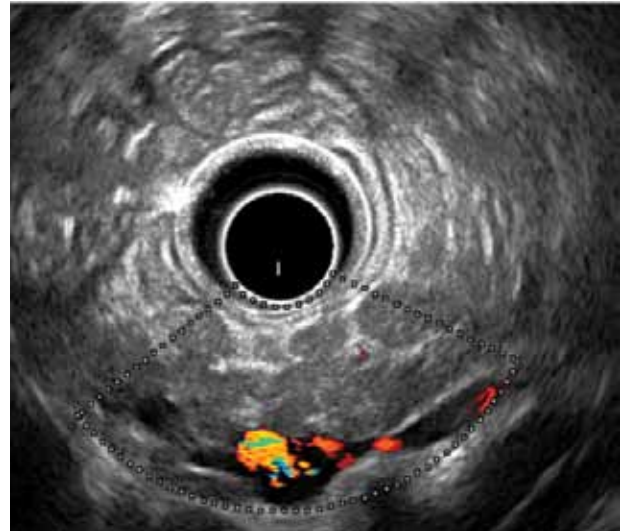
**Figure 2** Endoscopic ultrasound showing gallbladder sludge

episodes of abdominal pain without elevation of pancreatic enzymes. The follow-up EUS reconfirmed the initial findings of chronic pancreatitis and 2/9 (22.2%) patients developed parenchymal calcification on follow up. The remaining 9 patients with normal pancreas subsequently remained well on a follow-up period of 5-36 months.

All the patients with common bile duct stones or sludge underwent ERCP and biliary sphincterotomy 1-5 days after EUS examination and the presence of stones or sludge was reconfirmed in all the patients. Similarly, the patients with gallbladder sludge/calculi underwent elective cholecystectomy 8-28 days after the EUS examination and presence of stones was confirmed in all the patients. Out of 13 patients with gallbladder sludge, on surgery sludge-like material was observed in 10 patients and all these 13 patients had histological evidence of chronic cholecystitis. None of these patients had recurrence of pancreatitis after elective cholecystectomy. The pancreas



**Figure 3** Endoscopic ultrasound showing small tumor in the pancreatic head blocking the main pancreatic duct



**Figure 4** Endoscopic ultrasound showing changes of chronic pancreatitis

divisum was reconfirmed on subsequently performed ERCP and this patient underwent minor papillotomy and has been asymptomatic thereafter.

## Discussion

EUS is an important diagnostic modality for evaluation of patients with pancreaticobiliary abnormalities. In our series of 40 patients with IAP, EUS could establish diagnosis in 22 (55%) patients. Conferring to the other major series [9-11], an underlying biliary abnormality was the most commonly identified pathology (50%) on EUS in our cohort of patients as well.

Biliary sludge, identified as low-level echogenic material without acoustic shadowing that gravitate toward the dependent portion in the gallbladder and move with positioning, was the most common cause identified by EUS in our series. EUS is highly precise in detecting biliary microlithiasis due to the following reasons: i. gallbladder is closely related to the stomach and duodenal wall; ii. the median distance between the echoendoscopic transducer and the gallbladder is small (0.5 mm); iii. the whole gallbladder (infundibulum, body and fundus) and cystic duct are examined, even under severe conditions of pancreatitis; and iv. the use of frequencies of 5.0, 7.5 and 12 MHz intensifies details in the images. Four of our patients with identified biliary pathologies had stones in gallbladder (n=3) and bile duct (n=1). These stones have not been picked up by the previous radiologic imaging. Although transabdominal US remains the diagnostic modality of choice in detecting stones in gallbladder, it may miss the gallbladder delineation in a sizeable proportion (up to 31%) of patients with AP during the first week of examination [12]. Zhan et al studied the utility of EUS in diagnosing unexplained biliary pathologies in 33 patients with mild acute biliary pancreatitis. The etiology of biliary pathology remained obscure in all of them even after thoroughly investigating them with transabdominal US, CECT

and MRCP. EUS picked up a biliary pathology in 42.5% of cases. Gallstones of size varying from as small as 2.2 mm to 5.2 mm and biliary sludge, were missed on previous imaging [13]. A number of studies have compared the accuracy of EUS to transabdominal US, ERCP, CT, and MRI/MRCP for detecting common bile duct stones [14-17]. In most reports, the sensitivity of EUS ranged from 88-97% with a specificity of 96-100%, comparable to that of ERCP.

Another important issue in patients with AP is whether the gallbladder sludge observed on EUS is the cause of the inflammatory process or the consequence of biliary stasis in patients who are fasting for an extended period because of the underlying disease. To overcome this, it is proposed that EUS examination should be delayed until the time when the patient starts eating normally. Likewise, in our study, the EUS examination was done at least 1 month after the attack of pancreatitis when the patients were pain-free and were eating normally. Also, all of our patients with gallstone disease and biliary sludge remained recurrence-free after cholecystectomy. However, delaying EUS for 4 weeks also has concerns like missing a small pre-papillary stone that can trigger a new attack of pancreatitis and delayed diagnosis of a small pancreatic tumor [18].

One interesting issue in our study is that there were no identified cases of choledochal cyst, anomalous biliopancreatic junction, intraductal papillary mucinous neoplasm (IPMN) etc. as the cause of IAP. This may be due to the strict inclusion criteria that we followed. Only those patients with unrevealing blood investigations (serum calcium, serum iPTH, and serum triglycerides), transabdominal US, CECT abdomen and/or MRCP were considered for EUS. Also patients with IAP may have underlying autoimmune pancreatitis [19], we did not observe any patient with autoimmune pancreatitis.

Pancreatic cancer can present with AP in a small percentage of cases [20,21]. EUS is highly sensitive in diagnosing very small tumors in the head of pancreas [22,23]. Tandon et al noted pancreatic cancer in 3.2% of IAP upon EUS examination [24]. Our patient had a 4 mm size tumor in the head of pancreas that was missed on prior radiologic imaging and could only be visualized by EUS. Thus, EUS is the modality of choice to detect small pancreatic tumors and should be considered especially in patients >40 years of age even after a negative cross-sectional imaging [25].

Although chronic pancreatitis (CP) may be diagnosed by various imaging modalities (transabdominal US, CECT, MRI/MRCP, ERCP), EUS is presently considered the most sensitive technique in diagnosis of CP [26,27]. Recently Catalano et al presented the new "Rosemont" criteria for the EUS based diagnosis of CP based on various parenchymal and ductal changes [28]. But recent data has shown that Rosemont criteria may not improve the diagnostic accuracy and interobserver variability in diagnosing CP [29]. Some degree of changes consistent with CP may have already been established in patients clinically presenting with IAP [30,31]. Thus, CP may be an end result in a proportion of recurrent IAP or might have been mimicking as IAP at the initial presentation itself. Diagnosis of CP in the latter situation is limited by the poor sensitivity of the currently available investigations. A combination of ERCP, pancreatic

function tests and EUS is helpful in making the early diagnosis of CP in such cases [32-34]. However, EUS is a highly sensitive imaging modality and by using fewer EUS criteria the specificity decreases. Zimmermann et al, on comparison of EUS standard criteria with the histological findings from specimens obtained during surgery, found that usage of five or more EUS criteria was associated with sensitivity of 60% and specificity of 83%, and, when three criteria were used, that sensitivity increased to 87% but specificity decreased to 64% [35]. Likewise, in our study, by using three criteria we may be increasing the false positivity, but all our patients with early CP developed full blown CP on follow up with two patients developing calcification. None of our patients with early CP had calcification or ductal calculi in the initial EUS examination and three of nine patients developed ductal dilatation on follow up. These patients underwent pancreatic endotherapy for relief of pain and are asymptomatic thereafter over a follow-up period of 14-42 months.

Finally, we could not find a definite cause for IAP in 9 patients and none of them had a further recurrence. Additional investigations involving more invasive modalities like ERCP and SOM [36] may be helpful to identify other potential etiologies like sphincter of Oddi dysfunction, long common channel, pancreas divisum etc. Also, genetic linkage analysis may be carried out in this subset of patients to identify any of the known mutations in genes like PRSS1, SPINK/PSTI, and CFTR [37]. But taking into consideration that none of these 9 patients had further attacks of pancreatitis may indicate that they may not have had a serious underlying cause for their AP warranting these investigations.

In conclusion, we found an occult biliary pathology (microlithiasis and small stone) as the predominant cause of IAP and EUS is an important tool in evaluating IAP especially after an initial negative diagnostic workup.

### Summary Box

#### What is already known:

- Despite a thorough diagnostic workup, a definitive cause cannot be established in a variable proportion of patients of acute pancreatitis
- Since pancreas can be best visualized by endoscopic ultrasound (EUS), it seems to be an useful modality to investigate Idiopathic acute pancreatitis (IAP)

#### What the new findings are:

- EUS is an important tool in evaluating IAP especially after an initial negative diagnostic workup
- EUS can identify an underlying etiology in almost 50% of these patients
- Underlying biliary abnormality was the most commonly identified etiology on EUS in Indian patients with IAP

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