

Endoscopic sphincterotomy for acute relapsing pancreatitis associated with periampullary diverticula : a long-term follow-up

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Background and study aims : Periampullary diverticula (PAD) are extraluminal outpouchings of the duodenum arising within a radius of 2-3 cm from the ampulla of Vater. Data concerning the association of PAD with biliopancreatic disease are inconsistent, but an association between acute pancreatitis and PAD has been reported. The aim of this retrospective study was to evaluate the outcome of endoscopic sphincterotomy (ES) in a Greek cohort of patients with acute relapsing pancreatitis associated with PAD.

Patients and methods : A total of 344 patients who had undergone ERCP between 1994 and 2005 for investigation of acute pancreatitis were retrospectively entered into a database. Of these patients, 11 (3.19% ; median age : 69 years ; range : 58-78 ; 3 men, 8 women) were found to have acute relapsing pancreatitis associated with PAD. All patients underwent ES and were followed for new episodes of acute pancreatitis or other complications.

Results : No further episodes of acute pancreatitis occurred after ES, during a long-term follow-up (median : 4.3 years, range : 1.9-10.4). Two patients (18.2%) presented post-procedure mild pancreatitis and one patient (9.1%) post-ES stenosis with two small common bile duct stones and was treated with ES and extraction of stones.

Conclusion : ES is the treatment of choice for patients with acute relapsing pancreatitis associated with PAD. (*Acta gastroenterol. belg.*, 2007, 70, 163-166).

Introduction

Periampullary diverticula (PAD) are acquired extraluminal mucosal outpouchings of the duodenum arising adjacent to or containing the ampulla of Vater. Pathophysiologically, they are pulsion or traction diverticula and occur more frequently in elderly persons, with a prevalence range of 0.16% to 23% according to the various methods of investigation use (1,2,3). PADS are frequent incidental findings whose clinical significance has not been fully appreciated. Some investigators demonstrated an association of PAD with common bile duct stones (4-9), and other studies have found an increased prevalence of acute idiopathic pancreatitis (10,11), but a clear correlation between PAD and acute relapsing pancreatitis remains in debate. An extensive search in Medline, based on the keywords "acute pancreatitis" and "periampullary or duodenal diverticula" identified no reports on long-term follow-up of patients undergoing ES for acute relapsing pancreatitis associated with PAD.

The aim of this study was to investigate the influence of endoscopic sphincterotomy on the clinical course of patients with acute relapsing pancreatitis associated with PAD.

Patients and methods

The endoscopy databases of our tertiary referral centres were reviewed retrospectively in the period 1994-2005 to identify patients with acute relapsing pancreatitis and PAD. All patients had a history of cholecystectomy for cholelithiasis and absence of common bile duct stones or sludge on ERCP. The study was approved by our Hospitals Review Board.

All patients underwent a thorough evaluation that included past medical history, physical examination, routine laboratory tests, abdominal echo or CT and in three patients MRI cholangiopancreatography. None of the patients had hyperlipidemia or hyperparathyroidism. As acute relapsing pancreatitis was defined a clinical entity in which the patient suffered from acute pancreatitis (abdominal pain associated with at least three-fold increase of serum amylase) on more than one occasion.

Patients were defined as having acute relapsing pancreatitis associated with periampullary diverticula if there was a history of cholecystectomy, normal visualization of biliary tree in ERCP and absence of stones or biliary sludge on the sweeping of the common bile duct with a catheter-balloon or basket.

A periampullary diverticulum was defined endoscopically as a depressed lesion of 0.5 cm or more with intact mucosa and with major papilla either within it or close by (within 2-3 cm). The relative positions of the papilla and diverticulum were defined according to recognized criteria : a papilla arising within a diverticulum was called an intradiverticular papilla ; a papilla might be described as being at the edge of a diverticulum ; and a diverticulum within a 2 cm radius of the papilla was called a juxtapapillary diverticulum. A diverticulum was defined as small (diameter < 1 cm), medium (diameter 1-2 cm), or large (diameter > 2 cm).

An appropriate search for microscopic lithiasis or collection of bile from the duodenum via nasoduodenal tube placed by fluoroscopy or by upper gastrointestinal endoscopy or bile sampled during ERCP was not carried out.

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Each patient or his/her relatives gave written informed consent prior to endoscopic sphincterotomy (ES). All procedures were performed by experienced pancreatobiliary endoscopists who had performed more than 5000 therapeutic ERCPs and with annual volumes of more than 400 ERCPs. Procedures were performed with the patient in the oblique left lateral position using different types of Olympus duodenoscopes. During the procedure, sedation and analgesia were achieved with intravenous midazolam and meperidine titrated according to the age and tolerance of each patient. Bowel relaxation was achieved with intravenous administration of hyoscine butylbromide or glucagon. The patients were given continuous nasal oxygen and their haemoglobin saturation and pulse rate were monitored with pulse oximetry.

The therapeutic protocol included visualization of the biliary and pancreatic tree. If pancreatogram was normal, a biliary ES was performed, followed by sweeping of the common bile duct using balloon catheter or Dormia basket. The ES was performed with a double-lumen pull-type sphincterotome over a hydrophilic guide-wire to better control the cutting and to avoid the risk of perforation.

In general, it is routine in our units to perform ES by completely dividing the sphincter and by extending the incision to the maximum safe limit. As incision of the sphincterotomy to the maximum safety limit is defined the proximal hooding fold in cases of small papilla, or extending the cutting to include the visible intramural bile duct. We believe this minimizes the risk of subsequent sphincter stenosis.

Complications of ES were assessed according to consensus criteria by Cotton *et al.* (12) and defined as early (pancreatitis, bleeding, and perforation) or late (post-sphincterotomy stenosis or common bile duct stones development).

Clinical success of ES was defined as cessation of episodes of acute pancreatitis.

Follow-up was performed until patients' death or the writing of the study (April 2006) and was obtained through questionnaires (including standard definitions of criteria for complications, or new episodes of acute pancreatitis) mailed to the referring centres and general practitioners. Telephone calls to the patients or their relatives were also made whenever necessary.

Results

A total of 344 patients underwent ERCP for investigation of acute pancreatitis, between 1994 and 2005, in our referral centres. Of these, 11 patients (3.19%) with acute relapsing pancreatitis associated with periampullary diverticula for which sufficient data were available for this study were identified. All patients had a history of cholecystectomy.

The median age of patients was 69 years (range : 58-78 years). The male/female ratio was 3/8 (Table 1). A single diverticulum was evident in 10 patients (90.9%), while in one patient (9.1%) the major papilla was found between two medium size diverticula. In 8 patients (72.7%) the papilla was at the edge of diverticulum, in 2 patients (18.2%) the papilla was juxtapapillary and in one patient (9.1%) the papilla was inside the diverticulum (Table 1).

The majority of patients (n = 7) had a medium size diverticulum, 3 had large and in 1 patient the diverticulum was small (Table 1). The time interval between episodes of pancreatitis ranged 2 to 14 months (median 7 months).

The median time between cholecystectomy and first episode of acute pancreatitis was 3 years (range : 1-7 years), and the median number of episodes of acute pancreatitis were 2 (range : 2-3 episodes) (Table 1).

Table 1. — Clinical characteristics, outcome and complications of patients with periampullary diverticula undergoing ES

	N	%
Number of patients	11	100
Sex (male/female)	3/8	27.3/72.7
Median age (range) (yrs)	69 (58-78)	
Median time from cholecystectomy (range) (yrs)	3 (1-7)	
Median number of episodes of acute pancreatitis (range)	2 (2-3)	
Site of papilla		
at the edge	8	72.7
juxtapapillary	2	18.2
intradiverticular	1	9.1
Size of the diverticulum		
small	1	9.1
medium	7	63.6
large	3	27.3
Recurrence of symptoms	0	0
Complications		
early (mild pancreatitis)	2	18.2
late (post-ES stenosis plus CBD stones)	1	9.1
Median follow-up after ES (range) (yrs)	4.3 (1.9-10.4)	

ES : Endoscopic sphincterotomy ; CBD : common bile duct.

Mild post-procedure pancreatitis occurred in two patients (18.2%). This was defined as abdominal pain consistent with pancreatic origin in the setting of hyperamylasemia. Those patients responded well to conservative management and were discharged from the hospital within 72 hours. There were no episodes of post-ERCP perforation or cholangitis. A female patient presented with cholangitis two years after ES and post-sphincterotomy stenosis with two small common bile duct stones were found. She was treated with ES and clearing the common bile duct with Dormia basket. No patient required surgery for a complication and there were no procedure-related deaths. Four patients died during the follow-up period from myocardial infarction (n = 3) and cerebral stroke (n = 1). During a median follow-up of 4.3 years (range : 1.9-10.4 years) no recurrence of acute pancreatitis was observed.

Discussion

Any cause of acute pancreatitis, e.g. lithiasis, alcohol abuse, drug, metabolic condition or tumour, may lead to relapsing disease, if the original underlying factor is not corrected.

In our patients the metabolic conditions, such as hypocalcaemia or hyperlipidemia had been excluded as causes of pancreatitis, and the usual non-invasive imaging examinations (abdominal echo, CT and MRI cholangiography) did not reveal the underlying cause. All patients underwent ERCP since ERCP is generally recommended if a patient has two or more bouts of unexplained acute pancreatitis (13). We did not investigate the existence of microlithiasis or perform manometry to exclude sphincter's Oddi dysfunction. The term "biliary microlithiasis" typically refers to cholesterol monohydrate crystals and calcium bilirubinate granules finding on light microscopy of an endoscopically acquired centrifuged sample of bile (14). The criteria for differentiation between biliary microliths and small stones are not clear, but generally, a gallstone is defined as a particle with a diameter greater than 2 or 3 mm that cannot be crushed by digital compression (14). Considerable controversy exists over the clinical significance of biliary microlithiasis. Experts (14-20) disagree whether this is an innocent phenomenon or precursor in producing acute pancreatitis. Hypothetically, microlithiasis can lead to pancreatitis through a number of mechanisms. Small stones may transiently impact the papilla leading to pancreatic duct obstruction and pancreatitis (21). Moreover, recurrent passage of stones may lead to papillary stenosis or sphincter's Oddi dysfunction, both associated with acute pancreatitis (22).

PAD are acquired anomalies and occur more frequently in elderly persons, having a prevalence rate of 0.16 to 23%, according to the various methods of investigations used (1,2,3). The median age of our patients was 69 years (range 58-78 years). The relationship

between PAD and pancreatitis is a tenuous one. As PAD is associated with the presence of bile duct stones (4-9), it is difficult to tell whether pancreatitis is caused by bile duct stones or by the diverticula themselves.

As sphincter Oddi's muscle usually lies on the floor or the rim of the diverticulum it has been hypothesized that distension of a diverticulum with impacted food may cause compression of the pancreatic duct, resulting in pancreatitis.

There are case reports and anecdotal accounts implicating PAD in the pathogenesis of acute pancreatitis (4,11,23-26). PADS were found in 24% of 75 patients with acute pancreatitis in a retrospective study while only 4% of patients in a comparable control group had PAD (23). In a study of 470 consecutive patients undergoing ERCP, acute relapsing pancreatitis or chronic pancreatitis was found in 26% of patients with PAD and in 14% of those without PAD ($p < 0.05$) (27). Psathakis *et al.* found that 5 out of 50 patients with PAD had features of pancreatitis (23).

Sphincter's Oddi dysfunction secondary to PAD has also been implicated in the pathogenesis of acute pancreatitis (11,28). A recent study has suggested that PAD should be included as a factor in the aetiology of acute pancreatitis in the elderly and that the presence of PAD should be excluded before diagnosing idiopathic acute pancreatitis (11). No significant difference was noted when the proportion of patients with PAD and gallstone pancreatitis was compared with that with gallstone pancreatitis and no PAD (72% vs. 73% ; $p = 0.9$). However, when patients with idiopathic acute pancreatitis were analyzed, there was a significantly higher incidence in patients with PAD than in those without this condition (14% vs. 2% ; $p = 0.04$) (11). Leinoven *et al.* (10) found that patients with PAD developed acute pancreatitis twice as often as those without this condition (11% vs. 6%) but this difference was not statistically significant. Other studies (3,4) have been unable to establish that patients with PAD develop acute pancreatitis more frequently than those without PAD. Consequently, according to the reported data associating PAD and acute pancreatitis there is insufficient evidence to state categorically that PAD contribute significantly to the pathogenesis of acute pancreatitis.

As all our patients had undergone cholecystectomy some years ago (median : 4.3 years ; range : 1.9-10.4 years) for cholelithiasis, they had a predisposition to develop biliary stones. Despite no stones or biliary sludge were demonstrated on visualization of the biliary tree and on macroscopic examination after ES and sweeping of the common bile duct, we could not exclude the microlithiasis as a cause of acute relapsing pancreatitis because no specific examination for microlithiasis was performed. Moreover, we did not investigate our patients with sphincter's Oddi manometry to exclude sphincter's dysfunction, which occurs in 10% of post-cholecystectomy patients and is a well recognized cause of acute relapsing pancreatitis.

PADS have been found to be associated with an increased frequency of disorders of the biliopancreatic system due to dysfunction of the sphincter of Oddi. We believe that PAD, in our patients, had a significant contribution in the episodes of acute pancreatitis, contributing either in the development of microlithiasis or sphincter's Oddi dysfunction or obstructing the orifice of main pancreatic duct by impacted food in the cavity of the diverticulum. Our belief is strengthened by the fact that after ES no further episodes of acute pancreatitis occurred.

In conclusion, despite the fact that our study is retrospective and the number of patients is relative small, we suggest ES as the treatment of choice for patients with acute relapsing pancreatitis and PAD the sole abnormal endoscopic finding.

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