Therapeutic approach and prevention in recurrent acute biliary pancreatitis

Ann. Ital. Chir., 2010; 81: 177-181

Vincenzo Neri, Antonio Ambrosi, Alberto Fersini, Nicola Tartaglia

Department of Surgical Sciences, Division of General Surgery, University of Foggia, Polyclinic "Ospedali Riuniti", Foggia, Italy.

Therapeutic approach and prevention in recurrent acute biliary pancreatitis

OBJECTIVES: *Acute biliary pancreatitis (ABP) is caused by alteration of the papillary patency. The normal transpapillar flux and the cleaning of the common biliary duct (CBD) may prevent potentially avoidable recurrent pancreatitis.*
METHODS: *In the period September 1997/December 2008 we have treated 224 ABP (34 severe, 190 mild/moderate): 162 (72,4%) with the first attack, 62 (27,6%) with recurrent ABP (second or further attack). The patients with recurrent pancreatitis had not undergone, in the previous hospital stay elsewhere, the evaluation and, if necessary, the treatment of the papillary obstacle and /or CBD stones, sludge, etc. In our hospital all patients had undergone the treatment of ABP. The treatment was completed with cholecystectomy. All the patients, after the discharge, were introduced in a follow-up program (clinical and ultrasonoghaphic (US) control after 180 days and 1 year).*
RESULTS: *In the follow-up of recurrent pancreatitis we have controlled 35 patients (56%-27 lost). The results of the follow-up showed, beside the absence of recurrent acute episodes, the stable normalization of laboratory cholestasis tests and US control. The same controls in 78 patients (48,1%) with a first attack of acute pancreatitis resulted normal in absence of a new acute episode.*
CONCLUSIONS: *Recurrent ABP have been caused by persistent papillary obstacle. Therefore we confirm therapeutic validity of the instrumental control (US/MRCP) and the possible treatment of papillary or biliary lithiasic obstacle for the prevention of recurrent ABP.*

KEYWORDS: Papillary obstacle, Prevention, Recurrent pancreatitis.

Introduction

Recurrent acute biliary pancreatitis is caused by obstacle in the papillary patency with abnormal biliopancreatic flow. The papillary obstacle, caused by gallstones, biliary sludge, cholesterol cristals, sclerosis or edema, determines the biliopancreatic reflux in the pancreatic duct with consequent pancreatitis. Therefore, restoring the normal transpapillary flow and cleaning the common biliary duct (CBD) can prevent pancreatitis recurrences. This pathogenetic pattern of acute biliary pancreatitis (ABP) is by now widely documented [1-7]. The incidence of recurrent biliary pancreatitis is reported to widely vary between 30% and 60% in patients who did not undergo cholecystectomy and endoscopic sfincterotomy (ES), often with a short interval between the first and the second attack: 4-6 weeks [8-11]. The aim of this study is to evaluate the possibility and means to prevent recurrent acute biliary pancreatis.

Materials and methods

The study evaluated the patients with ABP admitted to our hospital in the period September 1997 - December 2008. We collected a total of 224 cases, including 190 (84,9%) mild/moderate and 34 (15,1%) severe pancreatitis. Among moderate pancreatitis, we recognized 27 (12%) moderate/severe pancreatitis, characterized by extensive pancreatic and peripancreatic inflammation

Pervenuto in Redazione Maggio 2010. Accettato per la pubblicazione Giugno 2010.
Corrispondence to: Prof. Vincenzo Neri, Via G. Murat 86, 70123 Bari, Italy (E-mail:v.neri@unifg.it).

with fluid collections and mild necrosis, without however impairment of the general conditions [11,12].
We selected, by the medical records, the patients who have had a first attack of acute pancreatitis, distinguishing them from the ones who had previously suffered from one or more episodes of ABP. The patients with a first attack of onset were on the whole 162 (72,3%), while those with previous repeated episodes were 62 (27,7%). Among the 62 recurrent pancreatitis, 8 (12,9%) were severe and 54 (87,09%) moderate/mild.
The acute episode of pancreatitis was defined by the presence of abdominal epi-mesogastric pain radiating through to the back and by increased serum amylase and lipase levels.
In all patients to establish gallstone etiology of pancreatitis we searched, on ultrasonography, gallbladder lithiasis and/or gallstones, sludge, microlithiasis etc. in the CBD or also the CBD size plus of 8 mm. Laboratory cholestasis tests were on average positive in 40% of patients: direct bilirubin between 2 and 5 mg/l, alkaline phosphatase plus 150 U/l and gamma-GT plus 200 U/l. Alcohol consumption in these patients had also been excluded.
The severity of the pancreatic involvement was assessed with abdominal ultrasound (US) at the admission and with computed tomography (CT) (Balthazar criteria) [13] after 48-72-hours (tab. I). The patients with previous attacks of recurrent acute pancreatitis don't have been submitted, during the previous hospitalizations, to any specific therapy for pancreatitis (endoscopic retrograde cholangiopancreatography (ERCP/ES, cholecystectomy), but only to simple supportive therapy.
According to medical records the first previous diagnosis of acute biliary pancreatitis, in the other hospitals, was based on clinical evaluation, serum chemistry tests, US, TC, MRCP.
In the group with recurrent pancreatitis control of gallstone etiology, laboratory cholestasis tests and the CT pancreatic involvement did not show dissimilar results in comparison to all patients.
All patients underwent the treatment for ABP, adjusted according to the degree of severity of the disease: intensive therapy, ERCP/ES (180/224=80%) within 72 hours from the onset in all severe pancreatitis (34) (in 3 cases this procedure was unsuccessful and in 7 cases it was delayed for 10 days), in all recurrent pancreatitis (62), in all moderate/severe pancreatitis (27) with extensive inflammatory pancreatic and peripancreatic involvement, fluid collection and mild pancreatic necrosis (as shown by CT), but without organ failure and finally in moderate/mild pancreatitis with laboratory cholestasis tests and US/MRCP confirmation of papillary obstacle (lithiasis, microlithiasis, sludge in CBD, papillary edema, stenosis, etc.) (57).
The treatment was completed with laparoscopic cholecystectomy: 218 video-laparocholecystectomies (VLC), 6 open cholecystectomies. The timing of cholecystectomy varied according to the severity of pancreatitis; generally, we waited for the stabilization of the pancreatic and peripancreatic phlogosis/necrosis and of the patient's general conditions.
All the patients, after the treatment and the discharge, were introduced in a follow-up program (clinical and US control after 180 days and 1 year).

TABELLA I - *Demographic data, Pancreatitis morphology (US/CT) in 224 acute biliary pancreatitis, at the ammission in our hospital.*

Mean age	Sex	
49 (40-86)	F 130 M 94	
Edematous	163	72.76%
Necrotizing	61	27.23%
Peripancreatic fluid collection	82	36.60%

Results

The 62 patients with recurrent pancreatitis, after the treatment (intensive therapy, antibiotics, ERCP/ES, cholecystectomy) and the discharge, entered a follow-up program with clinical and US controls at 180 days and 1 year. Thirty-five (56%) patients were monitored (27 patients could not be reached): the results of the follow-up showed, beside the absence of recurrent acute biliary pancreatitis, the stable normalization of laboratory and instrumental cholestasis tests at the first (180 days) and at the further control (1 year).
A further recurrence has occurred only in 1 patient (1/35 = 2,8%) with a moderate/mild pancreatitis at the 145th day from the discharge. Once the persistence of the papillary obstacle for incomplete sphincterotomy had been assessed, the resolution was obtained with medical therapy and a new ES. The same controls in 78 patients (78/162 = 48.1%) with a first attack of acute pancreatitis, at 180 days and 1 year from the discharge resulted normal, in the absence of new acute episodes.

Discussion

We believe that ES has a control role in the therapy of ABP. Biliary pancreatitis presents clinical findings of different severity. Signs and simptomys of reference, always verifiable, consist in epigastric pain with acute onset and characteristic radiation to the back and evident increase of serum amylase and lipase levels.
Moderate/mild pancreatitis, with pancreatic or peripancreatic edema, is not accompanied by impairment of the patient's general conditions, requires only supportive therapy and generally evolves towards a spontaneous

recovery. In these patients cholecystectomy is indicated and is performed, as a general rule, while the patient is still hospitalized. In moderate/mild pancreatitis ES is not generally indicated because the papillary obstacle is transient and probably incomplete. In the cases showing clinical and laboratory signs or ultrasound evidence of cholestasis, control of the bile duct with magnetic resonance cholangiopancreatography (MRCP) is proposed to use ERCP/ES only in therapeutic role, in case of lithiasic obstacles or biliary sludge in the CBD or papillary stenosis.

Moreover the advisability of the control of the bile duct with MRCP is discussed in patients with mild acute pancreatitis who do not show any clinical or instrumental sign of cholestasis, as an additional exam beside the routine abdominal ultrasonography before cholecystectomy.

The incidence of gallstones in the population of western countries is about 15% and among these patients about 10-15% have choledocholithiasis [14,14].

The literature data shows that a very variable range (45-75%) of patients with acute biliary pancreatitis is carrier of stones in CBD [16-18]. The cases with acute biliary pancreatitis include mild/moderate self-limiting forms with transient papillary obstacle, which are not accompanied by clinical, laboratory or US/TC signs of cholestasis. For these mild/moderate forms of acute pancreatitis the use of invasive procedures to explore the CBD is not advisable, while it is necessary to demonstrate the absence of stones in the CBD.

For these reasons in patients with mild/moderate acute biliary pancreatitis without increase of cholestasis indexes and in the absence of dilatation of intra and extrahepatic biliary ducts, it is useful to know if obstacles are present in the CBD. These patients should undergo a MRCP to determine the conditions of the CBD before cholecystectomy. In these cases, in fact, the extensive use of MRCP can be useful for a significant reduction of the number of non-therapeutic ERCP/ES and their associated complications.

The clinical scenario is, in 20-30% of cases, a severe pancreatitis characterized by extensive pancreatic and peri-pancreatic necrosis, fluid collections at risk of infection, possible systemic inflammatory response syndrome (SIRS) with compromission of the patient's general conditions which always requires starting immediately intensive therapy.

Besides, 20% of severe acute pancreatitis show an early severity - early severe acute pancreatitis [19] - with development within 72 hours of multiple organ failure and within 2 weeks infection of the pancreatic and peripancreatic necrotic collections with high mortality (40-60%). Thus, in all severe pancreatitis it is necessary the prolonged control of the pancreatic and peripancreatic necrotic collections which are exposed to infectious complications. Early (within 72 hours) ES has proved to be successful to maintain and to control the evolution of the inflammatory process and also safe to prevent close inflammatory-necrotic recurrences, which are caused by the persistence of the papillary obstacle and of the biliary reflux in the pancreatic duct [11,20-23]. Cholecystectomy is definitely indicated, but should be programmed once the patient's general conditions are stable.

Another clinical manifestation of biliary pancreatitis is the moderate form. Its nosographic definition is rather uncertain and difficult, placed between the much better identifiable mild and severe forms. Among the moderate forms it is significant, to therapeutic goals, to identify the moderate/severe forms [11] which are characterized by pancreatic necrosis, not exceeding 30% of the parenchyma at the CT control, edema and phlogosis of the retroperitoneal peripancreatic lodge with possible fluid collections. In these forms compromission of the patient's general conditions with multi-organ dysfunction is absent. Also, infection of the fluid collections occurs rarely.

The resolution of symptoms occurs in a relatively short time, 10 days on average; return to normality of serum amylase and lipase levels is slower and so is the resolution of the pancreatic and peripancreatic phlogosis/necrosis and the fluid collections reabsorption.

Also in these cases early (within 72 hours) ES is effective to reduce the risk of an often even early recurrence of pancreatitis. Cholecystectomy can be performed when the patient's general conditions are restored, almost always during the same hospitalization.

The pathogenesis of acute biliary pancreatitis is based on the alteration of transpapillary flow caused by edema and/or mechanical obstacle which determines the pancreatic intra-ductal reflux.

Thus ES by normalizing the biliopancreatic transpapillary flow removes the morphofunctional alteration and reduces the risk of pancreatitis recurrences, which present themselves sometimes with acute close episodes. Besides, ERCP/ES allows contextually to clean the CBD in case of sludge, microlithiasis or stones.

Once the initial pathogenesis has been defined, it remains to establish which patients with acute biliary pancreatitis should undergo ES. ES is indicated in severe, in moderate/severe pancreatitis, and, of course, in acute recurrent pancreatitis, in disregarding the presence of laboratory, clinical and US/MRCP signs of cholestasis or of a lithiasic obstacle in the CBD which, if present, constitute further motive for ES.

On the contrary moderate/mild pancreatitis does not require endoscopic treatment unless cholestasis is present.

In patients with recurrent pancreatitis, according to the pathogenetic sequence papillary obstacle / biliopancreatic reflux, the necessity to restore the papillary patency with ES is assumed.

In our experience recurrent pancreatitis is present in 30% of acute biliary pancreatitis treated. Recurrent pancreatitis occupies a nosographic place which presents a special interest because it can represent the connection between acute pancreatitis and chronic pancreatitis. At present the distinction between acute and chronic pan-

creatitis is in a phase of critical revision, whereas in the past the separation between the two forms regarding their pathogenesis and evolution was distinct.
A relevant contribution to the definition of the therapeutic choice and of the possible nosographic organization which may clarify the possible evolutions of acute pancreatitis (ex: recurrent acute pancreatitis evolving in chronicization of the phlogistic lesions) may come from the careful and extended clinical observation integrated with US-CT-MRCP verifications.
In fact, ever since its onset, we can consider pancreatitis as a difficult disease to classify, whose possibilities of evolution can be influenced by numerous etiopathogenetic factors and which should be subject to a dynamic follow- up.
Acute pancreatitis can evolve in the chronic form as the result of recurrences of repeated episodes of papillary obstruction secondary to edema and to sclerotic evolution of the inflammatory reaction of the Oddi sphincter. Biliary lithiasis, with passage of stones, biliary sludge, microstones or with persistent lithiasic obstacle at papillary level, plays a considerable role in the genesis of the sclerosis of the Oddi sphincter.
In this light, ES in the treatment of recurrent acute biliary pancreatitis may have a role of prevention against a hypothesized papillary fibrotic evolution of the phlogosis with consequent chronicization. The process that brings to pancreatic fibrotic alterations corresponds clinically to repeated episodes of typical abdominal pains and increased levels of serum amylase and lipase which are caused by recurrences of acute pancreatitis.
However, it is also possible that these episodes of parenchymal phlogosis evolve towards the self-limitation of the phlogosis without sequels, as an alternative to the evolution towards chronicization.
In a general anatomopathological picture, pancreatitis is an inflammation of the glandular parenchyma with destruction of its components. The possibilities of evolution of this process are self-limitation, progression with self-digestion and extensive necrosis of the parenchyma and of the surrounding tissues, or an evolution with predominance of fibrosis and calcifications which characterize chronic inflammation.
In conclusion, the point of correlation between acute and chronic pancreatitis is actually recurrent pancreatitis which presents itself with the anatomopathological substrate of an acute inflammatory focus during the course of chronic pancreatitis.
Finally, ES plays a double preventive role, interrupting the recurrence of acute attacks and the possible chronicization of the phlogistic process.

Conclusions

Recurrent acute biliary pancreatitis has been caused, in patients discharged from the hospital without additional treatment, by persistent papillary obstacle (small stones, sludge, microlithiasis, cholesterol crystals).
Therefore we confirm the therapeutic validity of US/MRCP control and the possible treatment (ERCP/ES) of papillary or biliary lithiasic obstacle for the prevention of recurrent acute biliary pancreatitis. ES plays an important role in the treatment of ABP and a most important role in recurrent pancreatitis because of the persistent papillary obstacle. In severe, moderate/severe and recurrent pancreatitis, US/MRCP confirmation of papillary obstacle is not necessary because this is persistent. On the contrary, in mild/moderate pancreatitis laboratory, US and MRCP confirmation of papillary or CBD lithiasic obstacle is useful prior to ERCP/ES because the papillary obstacle is transient. Patients with mild/moderate pancreatitis without cholestasis indexes should undergo instrumental control with MRCP for lithiasic obstacles in the CBD prior VLC because a very variable range (45-75%) of acute biliary pancreatitis is carrier of stones in the CBD. The results of this retrospective study show the efficiency of the therapeutic program with ERCP/ES in the prevention of recurrent acute biliary pancreatitis with mini-invasive approach.

Riassunto

La pancreatite acuta biliare è causata da un'alterata pervietà papillare. Ristabilire il normale flusso transpapillare e il cleaning dell'epatocoledoco possono prevenire le ricorrenze della pancreatite.
Nel periodo Settembre 97 / Dicembre 2008 sono state trattate 224 pancreatiti acute biliari (34 severe, 190 lievi/moderate): 162 (72.4%) al primo episodio, 62 (27.6%) con pancreatite acuta biliare ricorrente (secondo o successivi episodi). I pazienti con pancreatite ricorrente non erano stati sottoposti, durante il precedente ricovero in altro ospedale, al controllo e all'eventuale trattamento dell'ostacolo papillare o di calcoli o sabbia nella via biliare principale. Nel nostro ospedale tutti i pazienti sono stati sottoposti al trattamento della pancreatite acuta biliare con ERCP/ES e cleaning della via biliare principale completato, a distanza di alcuni giorni, con la colecistectomia. Tutti i pazienti dopo il trattamento e la dimissione sono stati sottoposti ad un programma di follow-up (controllo clinico e strumentale) dopo 180 giorni e 1 anno. Nel follow-up sono stati arruolati 35 pazienti (56%). I risultati del controllo a distanza hanno dimostrato, al di là di assenza di episodi acuti di pancreatite, la normalizzazione stabile degli indici di colestasi, di laboratorio e strumentali. Gli stessi controlli in 78 pazienti (48.1%), con un primo attacco di pancreatite acuta, sono risultati normali in assenza di nuovi episodi acuti.
La pancreatite acuta biliare ricorrente è causata dal persistente ostacolo papillare, pertanto possiamo confermare la validità terapeutica del controllo strumentale

(US/MRCP) e il possibile trattamento dell'ostacolo papillare o biliare litiasico per la prevenzione della pancreatite acuta biliare ricorrente.

References

1) Opie EL: *The aetiology of acute hemorrhagic pancreatitis.* Bull Johns Hopkins Hosp, 1901; 12:182-88.

2) Acosta JM, Ledesma CL: *Gallstone migration as a cause of acute pancreatitis.* N Engl J Med, 1974; 290:484-87.

3) Kelly TR: *Gallstone pancreatitis: Pathophysiology.* Surgery, 1976; 80:488-92.

4) Mayer AD, et al.: *Operations upon the biliary tract in patients with acute pancreatitis: Aims, indications and timing.* Ann R Coll Surg Engl, 1984; 66:179-83.

5) Armstrong CP, et al.: *The biliary tract in patients with acute gallstone pancreatitis.* Br J Surg, 1985; 72:551-55.

6) Lee Sp, et al.: *Biliary sludge as a cause of acute pancreatitis.* N Engl J Med, 1992; 326:529-93.

7) Ros E, et al.: *Occult microlithiasis in "idiopatic" acute pancreatitis; Prevention of relapse by cholecystectomy or ursodeoxycolic acid therapy.* Gastroenterology, 1991; 101:1701-709.

8) Kelly TR: *Gallstone pancreatitis: The timing of surgery.* Surgery, 1980; 88:345-50.

9) Paloyan D, Simanowitz D, Skinner DB: *The timing of biliary tract operations in patients with pancreatitis associated with gallstones.* Surg Gynecol Obstet, 1975; 141:737-39.

10) Steinberg W, Tenner S: *Acute pancreatitis.* N Engl J Med, 1994; 330:1198-210.

11) Heider TR, Brown AB, Grimm IS, et al.: *Endoscopic Sphyncterotomy permits internal laparoscopic cholecystectomy is patients with moderately severe gallstone pancreatitis.* J Gastro Surg, 2006; 10:1-5.

12) Nealon WH, Bawdamiak J, Walser EM: *Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone pancreatitis associated acute pancreatitis with peripancreatic fluid collections.* Ann Surg, 2004; 239:741-51.

13) Balthazar EJ, Robinson DL, Megibow AJ, et al.: *Acute pancreatitis: Value of CT in establishing prognosis.* Radiology, 1990; 174:331-36.

14) Tazuma S: *Gallstone disease: Epidemiology pathogenesis and classification of biliary stones (CBD and intra-hepatic).* Best Res Clin Gastroenterol, 2006; 20(6):1075-83.

15) Evarhart JE, Khare M, Hill M, et al.: *Prevalence and ethnic differences in gallbladder disease in the US.* Gastroenterology, 1999; 117:632-39.

16) Barro J, Soetikno RM, Carr-Locke DL: *Early endoscopic in acute pancreatitis: Is it indicated advisable, not indicated, or contraindicated? A proposal for clinical practise.* In Dominguez-Numoz JE, ed. *Clinical Pancreaotology for practising Gastroenterologists and Surgeons.* 1st ed. Oxford: Blackwell, 2005; 113-24.

17) Young YP, Lo SF, Yip AW: *Role of ERCP in the management of predicted mild acute biliary pancreatitis.* Asian J Surg, 2003; 26:197-201.

18) Stone HH, Fabian TC, Dunlop WE: *Gallstone pancreatitis. Biliary tract pathology in relation to time of operation.* Ann Surg, 1981; 194:305-12.

19) Beger HG, Rau BM: *Severe acute pancreatitis: Clinical course and management.* World J Gastroenterol, 2007; 13:5043-51.

20) Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP: *Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones.* Lancet, 1988; 2:979-83.

21) Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J: *Early treatment of acute biliary pancreatitis by endoscopic papillotomy.* N Engl J Med, 1993; 328:228-32. PubMed.

22) Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W: *Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis.* N Engl J Med, 1997; 336:237-42. PubMed.

23) Chang L, Lo S, Stabile BE, Lewis RJ, Toosie K, de Virgilio C: *Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: A prospective randomized trial.* Ann Surg, 2000; 231:82-87.