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6

Recurrent Pancreatitis

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1. Introduction

The nosological definition of inflammatory pancreatic diseases appears rather difficult and uncertain, as proved by the great number of classifications which have been proposed in the last few decades, showing that the definition and classification of this disease is still under critical review. The reason is the reduced availability or, in the majority of the cases, the absence of histological findings which can be connected to a clinical picture that moreover is often subject to evolutions. A not negligible role in generating uncertainties is played by the very diversified territorial distribution of the various forms of pancreatitis: this provides to the different observers different and often hardly reconcilable experiences. Therefore, the succeeding classifications are based exclusively on clinical or laboratory data or on imaging exams. We can consider as stable references the basic anatomo-clinical correspondences. It is preliminarily acquired that the parenchymal phlogistic process recognizes its origin in the self-digestive effect of the same pancreatic proteolytic enzymes. Self-limiting parenchymal inflammation characterizes mild and moderate acute pancreatitis. Self-digestive processes of serious entity with parenchymal necrosis and peripancreatic fluid collections manifest themselves as severe acute pancreatitis (SAP). Finally, chronic pancreatitis is histologically characterized by fibrosis, sclerosis and calcifications. Historically, the rigorous and well-defined distinction between acute and chronic pancreatitis has represented for a long time the basis of classifications in which acute and chronic pancreatitis were substantially considered two different diseases but, in the course of time, important modifications have taken place. In fact, currently this distinction is in discussion due to the imaging of the main bile duct and of the duct of Wirsung and above all due to the more comprehensive, prolonged and detailed clinical observations which allow to estimate the sometimes long evolution of pancreatitis. These observations show that acute and chronic forms overlap (Bassi & Butturini , 2007). The onset and/or the acute manifestations of chronic pancreatitis are considered and also the acute pancreatitis which, because of the repeated acute episodes, evolve anatomo-clinically towards chronicity. Recurrent acute pancreatitis is characterized by several acute episodes which follow the first attack. On the whole, the risk of recurrence for pancreatitis with different etiology is contained (20-30%). On the contrary the patients who present a second attack have a much higher risk of further recurrences and therefore require a rigorous diagnostic investigation. Biliary lithiasis and excessive alcohol consumption are the more frequent causes of pancreatitis, reaching as a whole the total incidence of 80% (Barthet, 2001; Gullo et al, 2002). However, the frequency rate between

biliary and alcoholic etiology is subject to great variations in relation to geographic distribution. Moreover, even if with much contained frequency, numerous other causes of pancreatitis are recognized which may manifest as recurrent and which, on the whole, represent 20% of the total (Ferec & Maire, 2005; Hastier, 2005) : hereditary, metabolic pancreatitis (hyperlipidemia, hypercalcaemia, steroids), from neoplastic ductal obstruction (intraductal papillary mucinous neoplasms (IPMN), periampullary tumors,etc), from congenital anomalies (pancreas divisum, annular pancreas, anomalies of the biliopancreatic junction), from dysfunction of the sphincter of Oddi, from drugs and toxic substances, trauma and infections and finally post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Among all the various forms of recurrent pancreatitis, the conditions based on the obstruction of the flow of pancreatic secretions amenable to endoscopic treatment (ERCP-Endoscopic Sphincterotomy (ES)) are in evidence: biliary pancreatitis, dysfunction of the sphincter of Oddi, pancreas divisum. The object of our interest is the anatomo-clinical condition of recurrent pancreatitis. Pancreatic inflammatory diseases may evolve towards chronicity because of either the episodic increase of the phlogistic response and/or the recurrence of acute attacks. In pancreatitis with different etiopathogenesis it is useful to examine which are the possible different pathogenetic modalities of pancreatitis recurrence and its possible evolution. On the basis of the clinical presentation, acute pancreatitis, in particular those of biliary etiology, can be subdivided in mild, moderate and severe: the former, which include clinical forms of different relevance and extension, represent the majority of acute pancreatitis (75%). Severe forms constitute the remaining 25%. Among these an ulterior 20% is represented by forms of particular and sudden severity (early severe acute pancreatitis (ESAP)) (Beger & Rau , 2007). Pancreatitis incidence increases stably with the increase of the average age of population and with the increased incidence of biliary lithiasis and alcohol consumption. Unlike in chronic pancreatitis in which fibrosis does not revert and there is no total recovery with restoration of the original condition, patients with an attack of acute pancreatitis, particularly in mild/moderate forms, show an almost complete anatomical and functional recovery. However, there remains still the possibility of other recurrent attacks. The reason of this possible evolution can be recognized in at least two circumstances: either the initial and effective cause persists or it is not completely removed by the therapeutic intervention: biliary lithiasis or biliary sludge, cholelithiasis, inflammatory papillary stenosis, invariated alcohol consumption, tumors obstructing the main pancreatic duct. Also severe pancreatitis with extended necrotic parenchymal areas can evolve into chronic pancreatitis for successive stenosis of the main pancreatic duct. The possibility of the evolution of an acute inflammatory process into a chronic phlogistic condition returns therefore in evidence. The distinction between acute and chronic pancreatitis is based on the natural history, the characteristics of the clinical picture and the anatomo-pathological alterations. Acute pancreatitis starts out in patients with no history of related illness and with the possibility of a complete resolution especially in mild/moderate forms. On the contrary, the anatomical and functional recovery in severe forms can be compromised. Moreover in SAP with severe impairment of the general clinical conditions and important structural alterations, the prognosis is serious. In chronic pancreatitis the organ impairment and the persistence of painful symptomatology of moderate severity characterize the intervals between the acute attacks. However, the acute attack, both in acute and chronic pancreatitis, is characterized by acute onset and by very

similar symptoms. Therefore, in the absence of an histological exam and of prolonged observation, the distinction between the two forms may be difficult. Regarding this point, SAP and ESAP often with biliary etiopathogenesis and with impairment of clinical conditions, must be considered with attention. In fact, the acute onset in chronic pancreatitis and severe acute pancreatitis may be distinguished for the presence in the latter of a severe impairment of clinical conditions which impairs the prognosis. All these considerations contribute to establish a connection between acute and chronic forms. The inflammatory process underlying acute pancreatitis can resolve if the recurrence of acute episodes is interrupted in the early stages. But, if the conditions which determine the recurrence of the acute attacks persist, like for example papillary sclerosis or obstruction with reflux in the duct of Wirsung, then inflammation will be able to evolve into fibrosis and acute pancreatitis will evolve anatomically and clinically into chronic pancreatitis. Therefore, recurrent pancreatitis may be considered the clinical condition which constitutes the bridge between acute and chronic pancreatitis. In fact, pancreatic inflammation may show a chronic evolution through the recurrence of acute episodes. Thus it is important to establish through which anatomical alterations and how in the pancreatitis of various etiologies this evolution is determined.

2. Biliary pancreatitis

Pathogenetic modalities of recurrent pancreatitis are well evident in biliary pancreatitis. Recurrent acute biliary pancreatitis is caused by obstacle in the papillary patency with abnormal biliopancreatic flow. Papillary obstacle, caused by gallstones, biliary sludge, cholesterol cristals, sclerosis or edema, determines biliopancreatic reflux in the pancreatic duct with consequent pancreatitis. Therefore, restoring the normal transpapillary flow and cleaning the common bile duct (CBD) can prevent pancreatitis recurrences. This pathogenetic pattern of acute biliary pancreatitis (ABP) is by now widely documented (Frossard et al.,2008; Lee et al, 1992; Opie, 1901; Pandol SJ, 2006; Wang et al, 2009). The incidence of recurrent biliary pancreatitis is reported to widely vary between 30% and 60% in patients who did not undergo cholecystectomy and ES, often with a short interval between the first and the second attack: 4-6 weeks (Heider et al, 2006; Van Geenen et al, 2009). Our purpose is to evaluate the possibility and the means to prevent recurrent acute biliary pancreatitis. Detailed examination of an homogeneous series contributes to clarify the anatomo-clinical details. The study evaluated the patients with ABP admitted to our hospital in the period September 1997 - December 2010. We collected a total of 261 cases, mean age 49 (20-86), M 112 – F 149, including 203 (77,7%) mild/moderate and 58 (22,3%) severe pancreatitis (Tab 1). Among moderate pancreatitis, we recognized 31 (15,7%) moderate/severe pancreatitis, characterized by extensive pancreatic and peripancreatic inflammation with fluid collections and mild necrosis, without however impairment of the general clinical conditions (Heider et al, 2006; Nealon et al, 2004). We selected, through the medical records, the patients who had a first attack of ABP, 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 188 (72,3%), while those with previous repeated episodes were 73 (28%). Among the 73 recurrent pancreatitis, 12 (16,4%) were severe and 61 (83,6%) moderate/mild (Tab. 2).

MEAN AGE	SEX	Dir. BIL. < 2 mg/dl	Dir. Bil. 2-5 mg/dl	AST/ALT x3 iU/l	gamma-GT >200 iU/l	ALP >150 iU/l	CBD size (US)> 8 mm	Cholecystic Lithiasis
49 (20-86)	F 149 M 112	60.4%	39.6%	26.8%	59.9%	53.6%	40.7%	100%
EDEMATOUS			187			71.64%		
NECROTIZING			74			28.36%		
PERIPANCREATIC FLUID COLLECTION			95/261			36.39%		

Table 1. Demographic data, percentage incidence of biliary lithiasis and cholestasis tests, pancreatitis morphology (US/CT) in 261 acute biliary pancreatitis at the admission in our Hospital.

MEAN AGE	SEX	Dir. Bil. < 2 mg/dl	Dir. Bil. 2-5 mg/dl	AST/ALT x3 iU/l	gamma-GT >200 iU/l	ALP >150 iU/l	CBD size (US)>8mm	Cholecystic Lithiasis
54 (28-76)	F 44 M 29	47.2%	52.8%	31.2%	64.3%	59.4%	48.2%	100%
EDEMATOUS			54			73.97%		
NECROTIZING			19			26.03%		
PERIPANCREATIC FLUID COLLECTION			33/73			45.20%		

Table 2. Demographic data, percentage incidence of biliary lithiasis and cholestasis tests, pancreatitis morphology (US/CT) in 73 recurrent acute pancreatitis at the admission in our Hospital.

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. To establish the gallstone etiology of pancreatitis, we searched, in all patients, on ultrasonography, gallbladder lithiasis and/or gallstones, sludge, microlithiasis etc. in the CBD or also a dilatation of the CBD (>8 mm). Laboratory cholestasis tests were on average positive in 40% of patients: direct bilirubin between 2 and 5 mg/l, alkaline phosphatase >150 U/l and gamma-GT >200 U/l. Alcohol consumption in these patients had also been excluded. The severity of pancreatic involvement was assessed with abdominal ultrasound (US) at the admission and with computed tomography (CT) (Balthazar criteria)(Balthazar et al, 1990) after 48-72-hours. The patients with previous attacks of recurrent acute pancreatitis have not been submitted, during the previous hospitalizations, to any specific therapy for pancreatitis (ERCP/ES, cholecystectomy), but only to simple supportive therapy. In this group, with recurrent pancreatitis, control of gallstone etiology, laboratory cholestasis tests and the CT pancreatic involvement were not dissimilar compared to all patients. All patients underwent the complete treatment for ABP, adjusted according to the degree of severity of the disease: intensive therapy, clinical and instrumental monitoring of papillary patency,

ERCP/ES (209/261=80%) within 72 hours from the onset in all severe pancreatitis (58) (in 3 cases this procedure was unsuccessful and in 7 cases it was delayed for 10 days), in all recurrent pancreatitis (73), in all moderate/severe pancreatitis (31) 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 instrumental (US/MRCP) confirmation of papillary obstacle (lithiasis, microlithiasis, sludge in CBD, papillary edema, stenosis, etc.) (59/203, 29%). The treatment was completed with laparoscopic cholecystectomy: 254 video-laparocholecystectomies (VLC) and 7 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 clinical conditions. After the treatment and the discharge, all the patients were introduced in a follow-up program (clinical and instrumental control after 90 and 180 days). The 73 patients with recurrent pancreatitis, after the standard therapeutic program and the discharge, entered a follow-up program with clinical and instrumental controls at 90 and 180 days. Forty-two (57,5%) patients were monitored (31 patients could not be reached): the results of the follow-up showed, beside the absence of critical episodes, the stable normalization of laboratory and instrumental cholestasis tests at the first (90 days) and at the second control (180 days) (Tab 3). A further recurrence has occurred only in 2 patients (2/42 = 2,7%) 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.

Tot. Bil.	ALP	AST/ALT	Amylase	Lipase	gamma-GT	CBD size (US)	Recurrence
0.80 mg/dl	115 iU/l	24/50 iU/l	220 iU/l	110 iU/l	38 iU/l	6 mm	2 (2.7%)

Table 3. Recurrent acute biliary pancreatitis 42/73 (57.5%) : follow-up (180 days)
Cholestasis tests were on average normal.

The same controls in 88 patients (88/188 = 46,8%) with a first attack of acute pancreatitis, at 90 and 180 days from the discharge resulted normal, in the absence of new acute episodes (Tab 4).

Tot. Bil.	ALP	AST/ALT	Amylase	Lipase	gamma-GT	CBD size (US)	Recurrence
0.90 mg/dl	112 iU/l	28/40 iU/l	95 iU/l	158 iU/l	54 iU/l	5 mm	_

Table 4. Acute biliary pancreatitis 88/188 (46,4%) : follow-up (180 days)
Cholestasis tests were on average normal.

We believe that ES has a control role in the therapy of ABP. Biliary pancreatitis presents clinical findings of different severity. Signs and symptoms of reference, always present, 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 clinical 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, instrumental control of the bile duct with magnetic resonance cholangiopancreatography (MRCP) is proposed. ERCP/ES is used as therapy only in case of lithiasic obstacles or biliary sludge in the CBD or papillary stenosis. Moreover the advisability of an instrumental 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 (Tazuma, 2006). The literature data show that a very variable range (45-75%) of patients with acute biliary pancreatitis has stones in the CBD (Barro et al,2005; Young et al,2003). The cases with acute biliary pancreatitis include mild/moderate self-limiting forms with transient papillary obstacle, which are not accompanied by clinical, laboratory or instrumental 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 extra-hepatic 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 peripancreatic necrosis, fluid collections at risk of infection, possible systemic inflammatory response syndrome (SIRS) with impairment of the patient's clinical conditions which always requires starting immediately intensive therapy. Besides, 20% of SAP show an early severity – ESAP - with development within 72 hours of multiple organ failure and within 2 weeks of infection of the pancreatic and peripancreatic necrotic collections with high mortality (40-60%). Thus, in all severe pancreatitis it is necessary a 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 (Folsch et al, 1997; Heider et al, 2006; Hernandez et al, 2004; Kimura et al, 2006; Neoptolemos et al, 1988; Sungler et al, 2007 ; Van Geenen et al, 2009). Cholecystectomy is definitely indicated, but should be programmed once the patient's clinical conditions are stable. Another clinical manifestation of biliary pancreatitis is the moderate form. Its nosological definition is rather difficult and uncertain, 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 (Heider et al,2006) 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 impairment of the patient's clinical 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 earlier recurrence of pancreatitis. Cholecystectomy can be performed when the patient's clinical 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 allow at the same time 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 and in moderate/severe pancreatitis, and, of course, in acute recurrent pancreatitis, irrespective of the presence of laboratory, clinical and instrumental 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. A relevant contribution to the definition of the therapeutic choice and of the possible nosological organization which may clarify the possible evolutions of acute pancreatitis (ex: recurrent acute pancreatitis evolving to chronification of the phlogistic lesions) may come from the careful and extended clinical observation integrated with repeated instrumental verifications: US-CT-MRCP. 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 into 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 sphincter of Oddi. Biliary lithiasis, with passage of stones, biliary sludge, microstones or with persistent lithiasic obstacle of the papilla, plays a considerable role in the genesis of the sclerosis of the sphincter of Oddi. In this light, ES in the treatment of recurrent acute biliary pancreatitis may have a role of prevention against an hypothesized papillary fibrotic evolution of the phlogosis with consequent chronification. 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. The episodes of parenchymal inflammation evolve towards the self-limitation of the phlogosis without sequels, as an alternative to the evolution towards chronification. The recurrent pancreatitis presents itself with the anatomopathological substrate of an acute inflammatory focus during the course of chronic pancreatitis. In a general picture, the possible evolutions of the pancreatic inflammations 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 phogosis. Finally, ES plays a double preventive role, interrupting the recurrence of acute attacks and the possible chronification of the phlogistic process. 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 instrumental control (US/MRCP) 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, instrumental 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 in a very variable range (45-75%) of acute biliary pancreatitis stones are present in the CBD. The results of these evaluations show the efficacy of the therapeutic program with ERCP/ES in the prevention of recurrent acute biliary pancreatitis with mini-invasive approach. The pathogenetic modalities of recurrent pancreatitis are well defined and obvious in the forms with biliary aetiology. However there are recurrent pancreatitis also among pancreatitis with different aetiology: these are less frequent pancreatitis for which a smaller number of observations is available and therefore with a somewhat uncertain characterization.

3. Alcoholic pancreatitis

The diagnosis of alcoholic pancreatitis is based on the definition of alcohol consumption and on the presence of anatomopatological alterations assessed with morphological examinations (X-rays, CT, EUS, wirsungraphy): parenchymal anomalies and of the excretory ducts with or without calcifications. In the course of alcoholic pancreatitis, recurrent episodes of acute pancreatitis can evolve into chronic pancreatitis and the effective and determining way of the recurrence of acute attacks can be evidenced (Gorelick, 2003; Spanier et al,2008; Whitcomb, 2005). In fact, most observers currently believe that chronic pancreatitis which follows prolonged ethanol abuse reflects repeated but subclinical, episodes of acute pancreatic injury. These repeated episodes of pancreatic injury with necrosis lead to fibrosis which characterizes chronic pancreatitis (Kloppel,1999). There are numerous theories since long presented in literature which propose an explanation of the lesive action of alcohol on pancreatic parenchyma but none of them is completely acquired. Alcohol would cause hypertriglyceridemia, fat acid and ethyl esters formation, that is formation of oxygen free radicals, causing pancreatic phlogistic damage. According to another hypothesis, alcohol alters the composition of pancreatic secretions with reduction of inhibiting enzymes and proteins precipitation forming intraductal plugs. Ductal obstruction causes increase in endoluminal pressure and consequent phlogosis with multiple foci of pancreatitis. Also the spasm of the sphincter of Oddi has been attributed to the action of alcohol.

4. Processes obstructing the flow of pancreatic juice, pancreas divisum

Obstructions of various nature of the main pancreatic excretory duct can cause pancreatitis too, in the parenchymal territory proximal to the obstruction. The obstacle can be a ductal neoplasia (IPMN) (Fazel et al ,2005) or a papillary alteration (periampullary diverticula, duodenal ulcer, duodenal Crohn, post-traumatic stenosis of the duct of Wirsung), or pancreas divisum (Arya et al, 2006; Gelrud et al, 2004). Pancreas divisum can cause acute pancreatitis for the small-caliber of the minor papilla which represents an obstacle to pancreatic flow. The endoscopic control of pressure in the pancreatic duct shows values more elevated than in normal patients. This hypothesis is at the basis of the therapeutic procedure of sphincterotomy of the pancreatic minor papilla. Therapeutic success reaches 80% (Bradley & Stephan,1996). The pancreatitis from ductal obstruction can present itself with an acute attack, orienting clinically to an acute form involving all the gland, but the histological characteristics are attributable to a chronic phlogosis which is limited to the portion of gland proximal to the obstruction. Also in this case, the evolution of the anatomo-pathological lesion is characterized by the sequence phlogosis-proteolisis-necrosis-fibrosis. In advanced stages of chronic pancreatitis ductal stenoses and gallstones can be the base of acute attacks of pancreatitis. However, recurrent acute attacks are documented also in the early stages of alcoholic chronic pancreatitis (Garg et al,2007). In summary, it is not well established whether initial chronic pancreatitis is the cause of recurrent acute pancreatitis or whether, on the contrary, acute recurrent attacks of pancreatitis evolve into chronic pancreatitis. In general, for pancreatitis caused by an obstacle to the flow of pancreatic secretions, the treatment consists in the removal of the obstacle. However, the specific treatment is deeply diversified according to the nature of the obstacle: ampullary and periampullary tumors and intraductal neoplastic stenoses must be removed surgically; small pancreatic stones or phlogistic stenosis can be treated with endoscopical procedures.

5. Hereditary pancreatitis

In hereditary pancreatitis (Ferec & Maire,2005; Whitcomb, 1999), the intraparenchymal activated trypsinogen is not inhibited by the antienzymes which are inactive for genetic causes, that is because it is present trypsin rendered genetically resistant to antitrypsin. The effect is a series of recurrent episodes of pancreatitis which induce parenchymal chronic alterations with fibrosis, calcifications and sclerosis.

6. Autoimmunitary pancreatitis

The autoimmunitary phlogistic process in pancreatitis is characterized by a sclerotic effect (Hamano et al, 2001) with conspicuous lymphoplasmacellular infiltrates. In these cases, phlogosis is delimited sometimes in a mass which, if in the pancreatic head, can cause biliopancreatic ductal obstruction, simulating a neoplastic lesion (autoimmune lymphoplasmacellular pancreatitis or eosinophilic pancreatitis).

7. Metabolic pancreatitis

Possible recurrences of acute attacks with phlogosis which evolve into fibrosis and chronic sclerosis occur for hypercalcaemia and hyperlipidemia. Hypercalcaemia (in

hyperparathyroidism) causes pancreatitis for the increased activation of proteolytic digestive enzymes. Hyperlipidemia causes pancreatitis because chylomicrons and free fat acids in excess interfere with pancreatic microcirculation. The circulatory alteration is the base of ductal obstructions of fibrous origin (obstructive mechanism).

8. Pancreatitis in celiac disease

Celiac disease (CD) is an immune mediated enteropathy caused by permanent insensivity to gluten in genetically susceptible individuals. Some recent reports have shown an association between acute pancreatitis and CD. A recent epidemiological study has shown that patients with CD have a higher risk than the general population for development of acute pancreatitis with epigastric pain and biochemical and radiographic confirmation (Ludvigsson et al, 2007). There are in the literature many pathogenetic mechanisms to explain the development of pancreatitis in patients with CD. T helper cell class 1 (TH1) cytokine up-regulation in CD may be predisposing factor for acute pancreatitis (Ludvigsson et al,2007). Another hyphotesis suggests that malnutrition can cause pancreatitis (Ludvigsson et al, 2007). However there is no evidence to show improvement of pancreatitis after correction for malnutrition. The mechanism for recurrent pancreatitis in CD may be papillary stenosis resulting from localized duodenal inflammation (Patel et al, 1999; Sood et al, 2007). The ES is the possible treatment. On the other hand it is also postulated that the improvement of recurrent episody of pancreatitis is a result of gluten restriction (Patel et al, 1999)).

9. Idiopathic pancreatitis

Idiopathic pancreatitis, that is with undefined etiology, represent approximately 20% of all cases. Among them, however, an important number can be ascribed to biliary forms with microstones or biliary sand of which there is no sure confirmation, that is they are caused by dysfunction of the sphincter of Oddi , generally of difficult demonstration.

10. Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction (SOD) can be due to stenosis or dyskinesia. Stenosis is a structural alteration due to inflammation and consequent stenosis (ex. passage of stones). Dyskinesia, instead, is a functional disorder with hypertonia. Stenosis or dyskinesia can involve the biliary sphincter, the pancreatic sphincter or the common sphincter. The clinical pictures may be slightly different if the alteration involves the biliary sphincter (pain of biliary type, biliary enzymes increase) or the pancreatic sphincter (pain of pancreatic type, recurrent attacks of pancreatitis). In summary, the phlogistic process is due to the obstruction and to the increased pressure in the pancreatic excretory system. The therapeutic indication in SOD is endoscopic sphincterotomy. Criteria for this diagnosis are represented by dilatation (> 8 milimeter) of the common bile duct, delayed emptying (more than 45 ') after ERCP, increased levels of alkaline phosphatase and gamma-GT during the episodes of pain. Certainty of diagnosis is based on finding, on manometry during ERCP, elevated pressure in the sphincter of Oddi (> 40 mmHG). Tc-99m iminodiacetic acid (IDA) cholescintigraphy is helpful for the diagnosis. It is moreover

possible that the dysfunction of the sphincter of Oddi be present also in patients who did not undergo cholecistectomy. Three levels of diagnostic certainty are distinguished. In type 1 SOD the three clinical criteria above mentioned are present and manometry of the sphincter is superfluous. In type 2 SOD two clinical criteria are present or or only one but this one must not be pain. In this case manometry of the sphincter of Oddi is necessary and is pathological in half of the cases. Lastly in type 3 SOD only pain is present in the right hypochondriac region. Manometry of the sphincter is necessary. Moreover, in these cases of uncertain assessment the answer to the sphincterotomy is not sure (Vassiliou & Laycock,2008). In fact endoscopic sphincterotomy, in particular of pancreatic sphincter, can prevent the recurrence of dysfunction of the sphincter of Oddi in 60% of cases (Elta, 2008).

In conclusion, the sequence of physiopathologic events which underlies pancreatic parenchymal phlogosis has overlapping characteristics in acute and chronic pancreatitis. The inflammatory process, caused by ductal obstruction or for cleansing, by the biliary reflux, of the mucosa of the main pancreatic duct, is determined by the action, in the acinar cells of pancreas, of the same proteolytic enzymes produced there. Chronic pancreatitis is caused by repeated episodes of subclinic acute pancreatitis with parenchymal necrosis evolving into fibrosis. Therefore, the hypotheses to consider are the activation of proteolytic enzymes and of trypsinogen in the same acinar cells or the reduced inhibitory action of antienzymes that is, in the end, the activated intraparenchymal diffusion of the pancreatic secretions activated in the lumen of the excretory duct for the alteration of its mucous barrier. Recurrent, also subclinical, episodes of acute pancreatitis with phlogosis and necrosis evolve into the fibrosis and the sclerosis of chronic pancreatitis. It must still be explained how the obstruction of the main pancreatic duct or of smaller ducts can induce the intracellular activation of proteolytic enzymes. Steer (Steer,1998) has advanced the hypothesis of the colocalization. According to this hypothesis, based on experimental data, enzymes like trypsinogen and lyisosomial hydrolase as catepsin B are localized together in the cytoplasmic vacuoli. In these conditions catepsin B can activate trypsinogen into trypsin which with its proteolytic action causes self-digestion and intraparenchymal phlogosis. The intensity of the inflammatory response can regulate the severity of pancreatitis.

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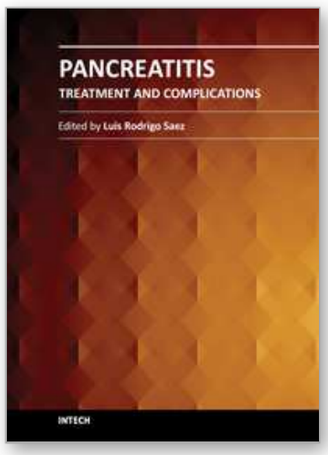
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Pancreatitis may be acute or chronic. Although they can be caused by similar aetiologies, they tend to follow distinct natural histories. Around 80% of acute pancreatitis (AP) diagnoses occur as secondary to gallstone disease and alcohol misuse. This disease is commonly associated with the sudden onset of upper abdominal that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10 to 25% of AP episodes are classified as severe, leading to an associated mortality rate of 7 to 30%. Treatment is conservative and consists of general medical support performed by experienced teams, sometimes in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has significant prognostic importance. Necrosis, hemorrhage, and infection convey rates of up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudoaneurysm formation, or venous thrombosis increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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