Chronic pancreatitis and pancreatic lithiasis.
State of the art

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Chronic pancreatitis and pancreatic lithiasis, isolated or associated, are infrequent diseases in western countries. They are linked to alcohol abuse, cigarette smoking, repeated episodes of acute pancreatitis and hereditary genetic factors. They are characterised by persistent or recurrent epigastric pain, digestive insufficiency, steatorrhoea, weight loss and secondary diabetes. They are easily diagnosed with CT and MRI ultrasound, but are difficult to treat. Medical therapy is symptomatic for diabetes and digestive failure. Invasive treatment is indicated only for pain that cannot be treated otherwise. For lithiasic forms, the therapeutic goal of removing stones can be achieved with shockwave and endoscopy, obtaining fragmentation and extraction of the stones. When this does not happen and these aids have proved ineffective, surgery must be used either as a partial or total resection of the afflicted pancreas, or as a derivation in the intestine of the pancreatic duct dilated and obstructed by Wirsung-jejunal anastomosis. These invasive treatments are effective in 80% of cases, but burdened with complications in 10% and relapses in 5%.

KEY WORDS: Chronic Pancreatitis, Chronic Pain, Pancreatic Lithiasis

Chronic pancreatitis and pancreatic lithiasis can be dealt with together because, despite having their own individual clinical-pathological features, they still represent two sides of the same coin: benign pancreatic pathologies, infrequent in western countries but which often also coexist, assuming causal profiles for each other.
Chronic pancreatitis is an inflammatory process of the pancreatic parenchyma which involves progressive replacement of the glandular tissue with fibrous tissue and consequent loss of the organ's exocrine and endocrine functions (Fig. 1). The inflammatory process is often associated with the formation of stones in the small and large ducts. It is difficult to determine whether the stones are the cause of pancreatitis or vice versa.

There are several causes of chronic pancreatitis including heredity, tropical environment, alcohol consumption, autoimmune processes, tobacco smoke, obesity and the presence of ductal stones [1], but in many cases no such cause is recognised.
The most reliable theories on the genesis of chronic pancreatitis include the hypothesis that the flow of bile due to sphincter of Oddi dyskinesia can be traced back to the Wirsung, and brings about an intraparenchymal inflammatory process that pushes the pancreatic acinar tissue and the epithelium to cover the ducts towards the fibrosis. The same effect on the parenchyma could be exerted by excessive alcohol consumption. A more recent theory considers acute pancreatitis and chronic pancreatitis as interconnected, with there being primarily an environmental or genetic predisposition to acute pancreatitis. A first acute episode would be the sentinel event, with subsequent development of an inflammatory state of the organ and production of stellate cells. Subsequent stimulations of these immune reactions would produce fibrosis and irreversible evolution of the pancreatitis towards chronicity [2].
As regards alcohol, it should be noted that only 3% of alcoholics develop chronic pancreatitis, therefore other

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Fig. 1: Chronic alcoolic pancreatitid.

Fig. 2: Multiple pancreatic stones.

causes must exist. Among these, fatty food and tobacco smoke have been identified, which obviously act with different mechanisms while producing the same negative result [3].

Tropical chronic pancreatitis appears to be linked to malnutrition, with particular reference to micronutrient deficiencies. Familial, hereditary or genetic pancreatitis would result from an autosomal, dominant familial mutation of the CFTR gene with incomplete penetration.

As for the causes of stone formation, alongside the coexistence of the parenchymal inflammatory process with consequent fibrosis of the ducts and difficulty excreting pancreatic juice, alcoholism and malnutrition should be mentioned. There have been descriptions of this pathology's association with hyperparathyroidism responsible for a serious alteration in the metabolism of calcium, also testified by nephrolithiasis. The stones are formed by chemical modification of the pancreatic juice due to alterations in its production, or due to the juice stagnating in the ducts owing to obstruction of the outflow path. The dysfunction leads to protein deposits in the ducts, where the calcium salts precipitate, forming stones. Alcohol is well known to cause a stimulation of the secretion, with lesion of the ductal epithelium and an increase in the concentration of proteins and calcium, from which lithiasis originates. The stones can be smooth and oval in the Wirsung or racemose in any small or large duct. They consist of calcium, phosphate, more often calcium carbonate or calcite, and fatty acids [4].

Chronic pancreatitis is only associated with pancreatic lithiasis (Fig. 2) in 20-30% of cases, and pancreatic lithiasis is not always associated with chronic pancreatitis. However, lithiasis is always associated with parenchymal inflammation.

This pancreatic disease is fairly rare in Italy and Europe, with two cases per 100,000 inhabitants. However, it is common in the east, especially in India and China, with a frequency of 200 cases per 100,000 inhabitants: 100 times higher than in our latitudes.

Clinically, this pathology is not always symptomatic. It may be discovered by chance during an ultrasound or radiological examination of the abdomen performed for a different reason. The symptomatology, when it exists, consists in 50-80% of cases of mainly epigastric abdominal pains, sometimes radiated posteriorly, that occur or worsen after eating and are associated with weight loss with diarrhoea and steatorrhoea. It has been attributed to ductal hypertension or neural inflammation or neurohormonal modifications [5].

Nausea and vomiting can be associated with the pain being re-exacerbated. This painful symptomatology, when present, and the effectiveness of the relative treatments, are reduced with the pathological process' progress towards chronicity. At other times, the telltale symptom may be insulin-dependent diabetes mellitus. This is a secondary diabetes often linked to obstruction of the Wirsung, with a consequent increase in intraductal pressure and ischaemia of the organ. This causes a blockage of the release of both digestive and glycoregulatory enzymes, due to the suffering of the islets of Langerhans. However, Beta cell function is better preserved than in type 1 insulin-dependent diabetes, with consequent better glycoregulation.

This frequent diabetes of obstructive pancreatic stones is less frequent in simple chronic pancreatitis. In such cases, a higher concentration of somatostatin has also been found, which may contribute to reducing blood glucose levels [6].

In the absence of painful symptoms, the residual clinical picture is generally well tolerated and a related neoplastic evolution has not been demonstrated.

Infrequent complications of chronic pancreatitis with or without lithiasis are pseudocysts, pancreatic fistulas, biliary obstructions with jaundice, difficulty in gastric emptying, ascites, pleural effusion and splenic phlebothrombosis. Each one has its own symptomatic process which is generally associated with the clinical picture of basic pancreatopathy [2].

Along with the clinical picture, diagnosis benefits from traditional aids [7]. In chronic pancreatitis, the level of enzymes in the blood, amylase, lipase, trypsin, elastase, can be normal or elevated, and especially in the initial stages are not demonstrative. The secretin stimulation test in patients with intestinal malabsorption conditions is more sensitive. The determination of fats in the stool is used to define malabsorption: it is normally equal to 7% of the ingested fats, but in chronic pancreatitis it can reach 90%. However, these results demonstrating exocrine insufficiency of the pancreas are no different between chronic pancreatitis and pancreatic cancer. Another discussion concerns diagnostic imaging, i.e. direct radiography of the abdomen, ultrasound, CT with and without contrast and magnetic resonance cholangiopancreatography with gadolinium; as well as gastroduodenal endoscopy and endoscopic ultrasound with biopsy, which can define the nature of the pathology and the location, size and number of stones where present. On imaging, the pancreas appears enlarged or more frequently atrophic, with irregular edges, cystic cavities, increased density, distortion and dilation of the main ducts with annular stenosis of the lumen (Fig. 1). When stones are present with computed tomography without contrast, their density can also be recognised, which would have a prognostic value for shockwave treatments (Fig. 2): in fact, a lower density would favour the best results [8]. Very good results can also be obtained by MRI (Figg. 3-4) especially for the study of the Wirsung duct. The indications for treatment in both chronic pancreatitis and pancreatic lithiasis derive from continuous or exceptional abdominal pain symptoms, and digestive insufficiency with weight loss and diabetes [9]. The therapy objectives are therefore to eliminate the pain, control the diabetes and eliminate any stones. In asymptomatic forms, abstention from any invasive treatment is agreed upon.

The available therapies are: symptomatic medical treatment based on the use of painkillers and antidiabetic agents, as well as digestive enzymes like pancrelipase which improves intestinal absorption, reducing malnutrition and weight loss [10]; endoscopy to remove the lithiasic obstruction of the Wirsung; shockwave lithotripsy to fragment stones anywhere in the pancreatic ductal tree; proper surgery with removal of the stones and intestinal derivation of the duct of Wirsung, or more or less complete removal of the organ. There have also been proposals of retroperitoneal infiltration for acupuncture with anaesthetic analgesic drugs for neurolysis and blockage of the celiac plexus, in cases where the pain is resistant to oral or parenteral analgesic therapy [11].

As for lithiasis, the therapeutic orientation in the absence of painful symptoms varies between no treatment, as proposed by many AAs such as Howell, Kalloo, Costamagna [12-14], and endoluminal therapy with pancreatoscopy and electrohydraulic lithotripsy as more recently introduced, supported by Beyna [15].

For the removal of the stones causing pain, the conditioning factors are: their size greater or less than 5 mm, their location in the small or large ducts, and the number of them. The general orientation is that the 0.5-1 mm calculations may not be treated or entrusted to an endoscopic extraction attempt (ERCP). Stones larger than 1 mm can be treated with shockwaves (ESWL) and ERCP performed in succession, first one then the other, with a variable order depending on the AA. Stones larger than 7 mm must be tackled with traditional surgery.

Non-surgical instrumental therapy for pancreatic lithiasis has undergone an interesting evolution in recent years. It is based on two different possibilities and instrumentations: the first is endovisceral endoscopic duodenum-bilio-pancreatic, with instruments introduced into the Wirsung after opening the papilla of Water; the other is external, with the use of shockwaves from the lithotripter.

In 2007 Dumonseau [16], on the basis of 55 cases subjected to shockwave, did not detect any difference in results with or without the association of endoscopic transduodenal papillotomy. In 2010 Tandan [17] after reviewing 1006 cases treated with shockwave and endotherapy, found a success rate of 76% and no complications.

In 2014 Ito [18] compared the positive results obtained with shockwave alone - 74% - with those obtained associating this endoscopy - 83% - or even the electrohydraulic treatment - 89%. Finally, in 2017 Bansal [19] recorded 100% success in 51 cases treated with balloon sphincteroplasty, complaining of single bleeding that stopped spontaneously. Encouraging results with pancreatoscopy were reported in 2017 by Pereira [20].

Years ago, it was proposed to use Trimetadione orally for long periods to pharmacologically dissolve the stones. Good results were reported, with a reduction in the size and number of stones in 70% of cases and beneficial effects on painful symptoms and diabetes [21]. It is an anticonvulsant drug that has been shown to be hepatotoxic and causes photophobia [22]: consequently it has not entered clinical practice.

Finally, proper surgical treatment of chronic pancreatitis and painful pancreatic stones should be mentioned. There are two type of intervention: demolition and conservation, the former being prevalent in simple chronic pancreatitis, the latter indicated when ductal stones are present [23].

Demolition interventions can be more or less extensive and have the purpose of removing the particularly sick, fibrotic, multinodular, multicystic part of the pancreas the pain originates from. Pancreatic resections can therefore be more or less extensive, but are generally caudal or left, also called distal splenopancreasectomies; on rare occasions they are right or duodeno-cephalic, configuring a classic pancreaticoduodenectomy; finally, they are sometimes total, with or without preservation of the duo-

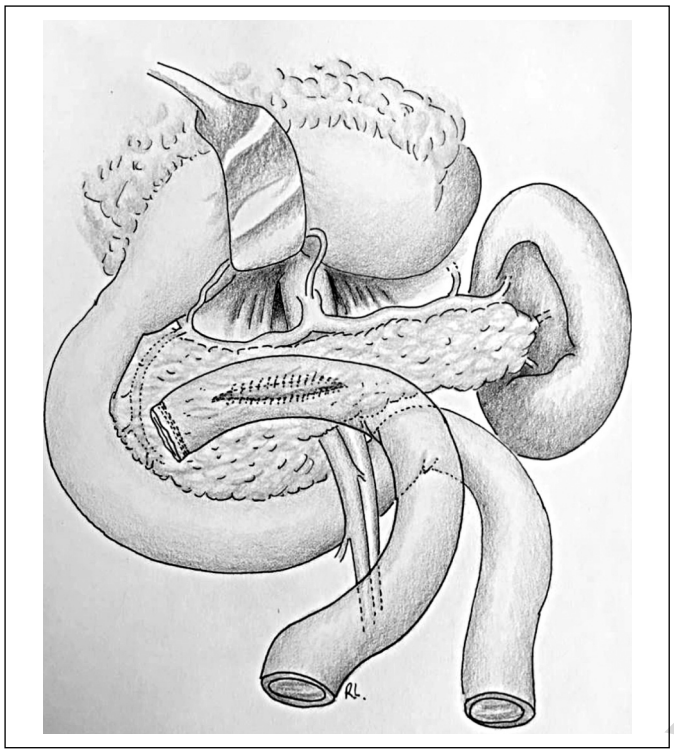

Fig. 3: Partington-Rochelle pancreato-jegiunostonomy.

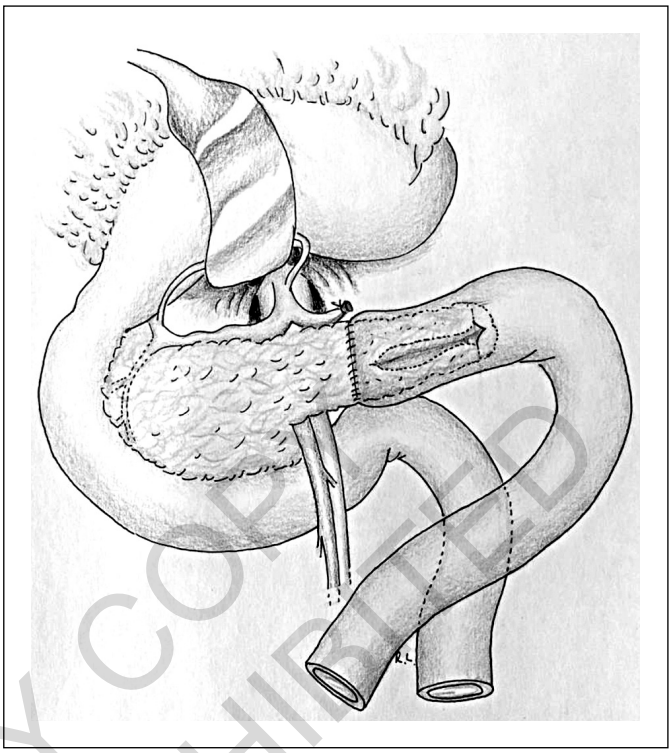

Fig. 4: Puestow Technique pancreato-jegiunostonomy.

denum [24]. In the former it is almost always necessary to remove the spleen, because chronic pancreatic inflammation is extended in the retroperitoneum well beyond the margins of the organ and it is often impossible to isolate the splenic vein, tenaciously incorporated; its ligation involves removing the spleen. These largely resective interventions on the left pancreas, where the islets of Langerhans are mainly located, cause serious insulin-dependent diabetes or aggravate pre-existing diabetes. For this reason, since it is a benign pathology, it was proposed to take the islets from the removed organ and use them for autotransplantation in the same patient's liver; this was subsequently implemented. Unfortunately, the results did not meet expectations [25].

In cases of painful stones, the first objective is conservative or derivative surgery with preservation of the organ and removal of the stones obstructing the main duct, considerably dilated with an internal condition of hyperpressure. The first choice intervention consists in axial opening of the Wirsung by several cm, with extraction of the greatest number of stones (Fig. 3). This may be impossible for those in the small ducts and especially those embedded in the part of the duct near the outlet in the ampulla of Water.

The reconstruction takes place with a laterolateral anastomosis on a jejunal loop mounted on the Roux, which guarantees that the pancreatic secretion is emptied even when the termination of the Wirsung remains obstructed, and consequently that the pain disappears. This method took the name of Partington-Rochelle, after the AAs who proposed it (Fig. 3).

A different technique but with the same purposes is the Puestow procedure [24], which involves removing a small part of the tail of the pancreas, enough to transversely reach the duct of Wirsung, where this has a sufficient calibre to allow small forceps in to extract the stones. The intervention is completed with a pancreatic-jejunal derivation through an end to end anastomosis between the caudal pancreatic stump and a Roux loop, with the same derivative purposes as the other technique.This technique has been proposed by Puestow (Fig. 4).

With these techniques, in 2001 Sakoras [26] boasted 81% success in 48 cases, while in 2016 Tan [24] achieved 90% in 297 cases. Fernandez Cruz [27] in 1997 reported a large series of 110 cases operated with surgical and clinical success with observation of 18 months. 35 cases had undergone duodenocephalo-pancreasectomy, 40 caudal body resection and 30 Wirsung jejunal anastomosis after removal of the stones.

The Japanese national review [28] is one of the most illustrative publications of the state of the art: it reports 1834 cases from 125 hospitals, of which 499 (27.2%) were not treated, shockwave plus endoscopy were used in 446 cases (24.3%), there was only endoscopic treatment in 261 cases (14.2%), and surgery in only 167 cases (9.1%). Different treatments were reserved for the other 358 cases (19.5%). Healing from painful symptoms occurred in 92.8% after surgery, 85.7% after shockwave and 80.8%

after endoscopy, but surgery had more complications in the short (27.1%) and long term (8.2%). Of the shockwave patients, 61 (14.6%) subsequently had to be operated on, as well as 32 (16%) of those treated endoscopically. The conclusion of the study is, in the first instance, in favour of shockwave because it is less invasive and burdened by fewer complications.

Our personal experience agrees with the attitude of abstention for asymptomatic forms of both simple chronic pancreatitis and lithiasis. In paucisymptomatic lithiasic forms with rare and short painful episodes, shockwave with ultrasound targeting seems preferable because it is less invasive, with possible subsequent endoscopic papillotomy if the crumbled lithiasic material cannot spontaneously pass through the papilla. In painful alithiasic forms, the choice of pancreatic resections is mandatory: they must be extended because a minimalist attitude may not solve the clinical problem, and force a more demolishing and more laborious second intervention with double the suffering and surgical risk for the patient. In painful lithiasic stones with dilation of the Wirsung in our case history too, the Partington-Rochelle intervention with toilet of the Wirsung and Wirsung-jejunal derivative anastomosis provided excellent results in the short term with no fistula and in the long term without the pain returning. Finally, it is of great interest to look at the technologies of the future, which have been opened up by pancreatoscopy associated with electrohydraulic or laser treatments in both stones and stenosis of the Wirsung.

Riassunto

Pancreatiti croniche e litiasi pancreatiche, isolate o associate, sono patologie poco frequenti nei Paesi occidentali. Sono legate all'abuso dell'alcol, al fumo delle sigarette, a ripetuti episodi di pancreatite acuta, a fattori genetici ereditari. Sono caratterizzate dal dolore epigastrico persistente o ricorrente, dalla insufficienza digestiva, la steatorrea, il dimagrimento, il diabete secondario. Sono facilmente diagnosticabili con ecografia TAC e RMN , ma sono difficilmente trattabili. La terapia medica è sintomatica per il diabete e per l'insufficienza digestiva. Il trattamento invasivo trova indicazione solo nel dolore non altrimenti trattabile. Per le forme litiasiche l'obiettivo terapeutico della rimozione dei calcoli si può raggiungere con le onde d'urto e con l'endoscopia ottenendo la frammentazione e l'estrazione dei calcoli. Quando ciò non avviene e questi presidii sono risultati poco efficaci, si deve far ricorso alla chirurgia sia come resezione parziale o totale del pancreas malato, sia come derivazione nell'intestino del dotto pancreatico dilatato ed ostruito mediante anastomosi Wirsung-digiunale. Questi trattamenti invasivi sono efficaci nell'80% dei casi, ma sono gravati da complicanze nel 10% e da recidive nel 5%.

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