Paraduodenal Pancreatitis: Many faces of the Same Diagnostic Challenge

Giovanni Valentini 1*, Monica Surace 1, Silvia Grosso 1, Annalisa Vernetto 1, Anna Maria Serra 1, Immacolata Andria 2, Dario Mazzucco 1

1 Gastroenterology Unit, Rivoli Hospital, Turin, Italy
2 Emergency Department, Maria Vittoria Hospital, Turin, Italy
*Correspondence should be addressed to Giovanni Valentini; valentinigiovanni73@alice.it

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Summary
Paraduodenal pancreatitis refers to an uncommon and still under-recognized form of recurrent or chronic pancreatitis that affects the so-called groove, the “theoretic” space between the pancreatic head and the duodenal wall.

Today, it still represents a diagnostic challenge; in fact, from a clinical point of view, its manifestations and complications can be numerous and different from each other. Despite modern imaging techniques, even in the most specialized centers, many untrained radiologists and gastroenterologists may encounter difficulty to make the proper diagnosis. In addition to descriptions of our case, a detailed review of current literature surrounding this clinical entity is provided in the article.

Keywords: Paraduodenal pancreatitis, Computed tomography, Endoscopy

Introduction

In 1970 Potet and Duclert described, for the first time, four cases of a new and distinct form of chronic pancreatitis manifesting as cystic dystrophy of the duodenal wall developing in heterotopic pancreas. By publishing these cases, they utilized the term “cystic dystrophy of the pancreas” [1], but it was discussed almost exclusively in European literature. In 1973 Becker drew attention to the existence of a localized chronic pancreatitis using the term Rinnenpankreatitis, in the German literature; subsequently, in 1982 Stolte et al. brought the term “groove pancreatitis” to the English literature, with the addition of other histologic features, such as Brunner gland hyperplasia and common bile duct stenosis [2]. Other terms to describe this distinct subset of pancreatitis, affecting predominantly the groove, have been used in the following years, including para-duodenal pancreatitis, duodenal cystic dystrophy, duodenal heterotopic pancreas and pancreatic hamartoma of the duodenum. Finally, in 2004 Adsay and Zamboni [3] proposed a universal name referred to as “paraduodenal pancreatitis” (PDP).

The term paraduodenal pancreatitis and groove pancreatitis are today used interchangeably, with all conditions having similar manifestations; they refer to an uncommon and still under-recognized form of recurrent or chronic pancreatitis that affects the so-called groove. The groove represents the potential space between the head of the pancreas, medially and the second part of the duodenum, laterally. It is bordered by the duodenal bulb and the third part of the duodenum in the superior and posteroinferior aspects, respectively. The inferior vena cava also forms the posterior aspect. Distal common bile duct (CBD), ampulla, major and minor papilla, superior pancreaticoduodenal vessels and lymphatics, as well as some lymph nodes, are anatomically present in the groove [4].

The most importance of PDP is that it can mimic pancreatic carcinoma, it may coexist with pancreatic carcinoma or even masks it and should be considered in the differential diagnosis of pancreatic masses or duodenal stenosis [5-7].
Today, PDP still represents a diagnostic challenge; in fact, from a clinical point of view, its manifestations and complications can be numerous and different from each other. Despite modern imaging techniques, even in the most specialized centers, many untrained radiologists and gastroenterologists may encounter difficulty to make the proper diagnosis. Only when careful consideration of clinical history, imaging studies, serology and cytologic features (if specimens are obtained) leads to high suspicion for PDP, conservative treatment is attempted, but patient must be closely and carefully followed up [8].

In addition to descriptions of our case, a detailed review of current literature surrounding this clinical entity is also provided in the article.

**Brief Clinical Case**

A 58-year-old male with a history of ischemic cardiomiopathy (two past myocardial infarctions treated with angioplasty), Arterial Hypertension, hypercholesterolemia and Diabetes Mellitus, was referred to our Unit for severe upper abdominal pain; a past history of alcohol abuse and smoking was reported. At admission physical examination revealed absence of jaundice, abdominal pain at palpation of epigastrium with no signs of peritoneal irritation. C reactive protein and white blood cells were elevated at laboratory tests, whereas serum pancreatic enzymes and liver function test, serum IgG4 level, Calcium, PTH, Triglyceride concentration and tumor markers (CEA and CA 19.9) were within normal range. Patient underwent erect abdominal radiography and abdomen ultrasound which resulted unremarkable. A contrast-enhanced CT of chest and abdomen ruled out aortic dissection, but showed circumferential thickening of the second part of the duodenum, with homogeneous enhancement of the thickened wall; multiple cysts were seen within the thickened wall determining duodenal lumen narrowing; the pancreatic head of the pancreas was bulky and heterogeneous (Figure 1A and 1B).

Hydratation, pain control (initially with morphin), proton pump inhibitors immediately started at admission, was continued; since the patient was not able to eat, parenteral nutrition was started too.

**Figure 1:** a and b. Contrast-enhanced CT of abdomen (axial section) showes a thickened duodenal wall and cysts withn it determining lumen narrowing; also seen is the leftward displacement of a normal appearing pancreatical-duodenal-artery (arrow), a key imaging finding to differentiate it from groove pancreatic carcinoma. c and d. MR Imaging. Paraduodenal cystic lesions are well seen on MRCP and T2-weighted axial MR image (arrow); smooth distal CBD stricture is also seen, along with non dilated pancreatic duct.
Esophagogastroduodenal endoscopy was performed after those imaging findings, confirming submucosal cystic changes in the duodenum, causing mucosal contour bulges and narrowing of bulb and second part of duodenum (Figure 2). Histological examination of duodenal biopsies was unremarkable. Paraduodenal pancreatitis with cystic dystrophy of duodenal wall was hypothesized.

A Magnetic Resonance Imaging was performed with Magnetic Resonance Cholangiopancreatography, which showed multiple cysts in the thickened wall of the duodenum; slight smooth narrowing of CBD was also seen; pancreatic duct was not dilated, while pancreatic head appeared slightly inhomogeneous due to an increase in fibrous component (Figure 1C and 1D).

The patient had improvement of his symptoms after clinical treatment directed to pancreatic rest, hydration, nutritional support and he went eating again; no more episodes of abdominal pain, nausea or vomiting were reported during hospitalization, so he was discharged with a close follow up planned and was encouraged to discontinue the use of alcohol and tobacco; he was symptom-free during the follow-up visit.

**Discussion**

Paraduodenal Pancreatitis (PDP) is an umbrella-term used for various conditions which previously had different names, including cystic dystrophy of pancreas, para-duodenal wall cysts, groove pancreatitis, pancreatic duodenal hamartoma, and myoadenomatosis.

As already discussed, the term paraduodenal pancreatitis and groove pancreatitis are today used interchangeably, with all conditions having similar manifestations; they refer to an uncommon and still under-recognized form of recurrent or chronic pancreatitis that affects the so-called groove, the “theoretic” space between the pancreatic head and the duodenal wall.

**Etiology and pathogenesis**

The etiology of PDP is likely heterogeneous and almost all authors agree that alcohol is the main predisposing factor and the main cause in all its clinical manifestations. One of the most frequently reported mechanisms is represented, in fact, by the altered pancreatic secretion through Santorini’s duct, related to aggression caused by alcohol.
When it is disturbed, the pancreatic secretion via the duct is directed towards the body of the pancreas, to Wirsung’s duct, which forms an acute angle, causing interference with the flow and an accumulation of temporal secretion at the top of the pancreatic head. The increased intraductal pressure in the Santorini’s Duct, on the other hand, facilitates the formation of pseudocysts and leakage of pancreatic juice into the groove [9]. This alteration can be caused by anatomical or functional causes [10]. Anatomical causes may be, mainly, represented by tumor occluding the minor papilla and Santorini Duct, a closed Santorini Duct, pancreas divisum and heterotopic pancreas in the duodenal wall (that may reflect incomplete involution of the dorsal pancreas in this area and contribute to obstruction of the flow). The heterotropic tissue, under the stimulation of tobacco and alcohol, can cause recurrent episodes of painful “ischemic” pancreatitis.

On the other hand, functional causes may be represented by dysfunction or occlusion of the minor papilla secondary to hyperplasia of Brunner’s glands and excessive chronic alcohol consumption and/or tobacco. Increase in intraductal protein concentration secondary to chronic alcohol consumption causes, in turn, increase in viscosity of the pancreatic juice, exacerbating the inflammatory process and ductal obstruction.

Peptic ulcers [11], both gastric and duodenal and previous biliary system illness, such as cholangitis have been postulated as potential triggers of PDP; we have, in fact published, in the form of abstract, a case of PDP (termed in our work Groove Pancreatitis) manifesting as a slow-resolution biliary pancreatitis, diagnosed after a cholecystectomy [12].

Gross (morphological and imaging) examination and classification

PDP can be classified morphologically as either a solid-mass occurring predominantly in and around the minor papilla (solid variant), or cystic lesions (cystic variant) within the pancreaticoduodenal groove or intramurally within the duodenal wall (Figure 3).

The solid variant is characterized by the presence of a sheet-like mass corresponding to the fibrous-scar, predominantly located in the pancreaticoduodenal groove; this variant has been traditionally described as ‘Groove Pancreatitis’ in literature and may be further subclassified into “pure” and “segmental forms”. In the “pure” form, scar tissue affects only the pancreatic groove, in the segmental form the scar tissue extends to the dorso-cranial portion of the pancreatic head, near the duodenal wall. In the “pure” form, in most cases, the pancreatic parenchyma and main pancreatic duct are not involved, while in the “segmental” form, the scarring tissue affects the dorso-cranial portion of the pancreatic head involving the main pancreatic duct, with chronic pancreatitis in addition to groove involvement [13]. However, the distinction between the two forms is not always clear-cut. The cystic variant of PDP is characterized by the presence of cysts in the duodenal wall (cystic dystrophy of the duodenum) and cysts within the pancreaticoduodenal groove (paraduodenal cysts) with or without inflammation, thickening and fibrosis of the duodenum. It may be associated with pancreatic heterotopias in the duodenal wall, as described for the first time by Potet and Dulcet in 1970 [1] and, in these cases, the cysts are commonly located in the second part of the duodenum. The cysts may not have an epithelial lining (in this case they are considered pseudocysts), although most of them have an epithelial lining resembling that of a normal pancreatic duct; hence they represent aberrant duct dilatations. In some cases, the heterotopias may not be true, as the ductal lining shows continuity with the dorsal pancreas and represents merely a continuation of the same [14]. It is still unclear and contentious whether Groove pancreatitis and cystic duodenal dystrophy are distinct entities or part of the same spectrum. Hence, the term “Paraduodenal Pancreatitis (PDP)” has been proposed to include Groove pancreatitis (solid subtype), cystic dystrophy of the duodenum and paraduodenal cysts (cystic subtype, [15,16]).

Clinical manifestations

Most patients with PDP are male, aged 40-60 years, with a history of chronic alcohol intake and, in a lower percentage, smoking. Severe abdominal pain (as in the case described), postprandial vomiting and weight loss, primarily due to duodenal obstruction, are the most common manifestations. About 80% of the patients with the clinical symptoms of acute pancreatitis present such high concentration of the serum amylase and serum lipase levels, although they may be in normal range when the illness affects predominantly the duodenal wall (as in our case). Tumor markers (CA 19-9 and CEA) are usually normal. It has also been reported that diarrhea or diabetes mellitus may be associated with PDP. The clinical symptoms of the syndrome spread over the time span ranging from few weeks to a year, then it becomes chronic with flare ups. We have recently described a case of solid variant (“groove pancreatitis”) manifesting, in fact, as recurrent episode of a previously diagnosed chronic pancreatitis [17]. Finally, in a high number of patients with alcohol abuse, obstructive jaundice has been observed in the course of chronic disease if late stenosis of CBD has occurred.

How to diagnose the disease

Preoperative diagnosis of PDP with its cystic and solid (Groove Pancreatitis) variant is a challenge. Depending
PARADUODENAL PANCREATITIS

CYSTIC VARIANT

Cysts with or without inflammation, thickening and fibrosis of the duodenum

Cysts in duodenal wall

CYSTIC DYSTROPHY OF DUODENUM

Cysts in pancreaticoduodenal groove

PARADUODENAL CYSTS

SOLID VARIANT

A solid–mass occurring predominantly in and around the minor papilla also known as GROOVE PANCREATITIS

PURE FORM

SEGMENTAL FORM

Figure 3: Morphological and imaging classification.
upon the clinical features, transabdominal ultrasound and upper gastrointestinal endoscopy are done as first-line examinations. Gastrointestinal endoscopy often shows an inflamed and polypoid duodenal mucosa with narrowing of the duodenal lumen or bulging of duodenal bulb (as in our case). Ultrasonography may show a hypoechoic mass with thickening of the duodenal wall, which causes narrowing of the second duodenal portion and, sometimes, bile duct obstruction [18,19]. Ultrasound findings depend on the stage of the disease, as postulated by Wronski [20] and reflect the different pathological process that occur during the evolution of PDP, especially of its solid variant. In the early stage, when inflammation predominates over fibrosis, a hypoechoic band is evident in the pancreatoduodenal groove. In the later stage, when fibrosis is established, hyperechoic thickening of the duodenal wall can be seen, with a pathognomonic finding sometimes observed: a hypechoicohic part of the pancreatic head with anechoic ductal structures (corresponding to proliferation of myoma to the adjacent pancreas).

CT scan is an excellent means for diagnosis of PDP and can reflect the histological characteristic of the disease; at CT examination (contrast-enhanced) PDP is seen as a hypoattenuating poorly enhancing soft tissue in the pancreatic-duodenal groove (solid variant); duodenal wall is frequently involved and thickened. This may be accompanied with cysts in the duodenal wall and/or the groove (cystic variant) [19,21]. Main Pancreatic Duct may exhibit mild dilatation in the body and tail region, whereas CBD may be constricted at its distal part leading to upstream dilatation. It should be emphasized that, even in extensive disease, the peripancreatic vessels, especially gastroduodenal artery (and its brach, pancreatic-duodenal artery) are preserved, showing no signs of thrombosis or infiltration (Figure 1A and 1B).

Some authors consider Magnetic Resonance Imaging and Magnetic Resonance Cholangiopancreatography (MRI and MRCP) the best diagnostic method for PDP, as it allows an evaluation of various aspects of the disease [9,22,23]. Fibrous tissue or cysts in the pancreatocduodenal groove, thickened and inflamed duodenal wall and/or duodenal wall cysts are commonly observed. Regarding the solid subtype, the most characteristic finding on MRI is sheet-like mass, corresponding to the fibrous scar in the groove; it is hypoointense in T1 in comparison with the pancreatic parenchyma [21], whereas in T2 sequence it may be hypoointense, isointense or slightly hyperintense, according to the duration of the disease. Cystic lesions may be identified in the groove or in the duodenal wall; they are obvious and hyperintense in T2 sequence and increased thickness or stenosis of the duodenal wall is often seen. CBD stenosis is frequently reported by some authors, though others observe it in only 50% of patients (when stenosis occurs it is smooth and tubular or presents a regular pattern of narrowing, as in our case, Figure 1C and D). MRCP, on the other hand, is currently the main imaging test used to visualize main pancreatic duct and CBD [24]. This technique shows the relationship between the ductal system and cystic changes and may reveal, as already mentioned, a smooth stenosis of the distal intrapancreatic portion of CBD. In the “pure” form of solid variant (Groove Pancreatitis) main pancreatic duct is normal, whereas in the “segmentary” form of the same variant it usually presents stenosis in the pancreatic head associated with a slight proximal dilatation. Most cases of PDP present a widening of the space between the pancreatic ducts, the distal CBD and the duodenal lumen, due to a space-occupying lesion in the groove, as well as a marked thickening of the duodenal wall.

Endoscopic ultrasound (EUS) represents one of the most sensitive methods for detecting pancreaticobiliary lesions and it is usually utilized for diagnosing PDP [5]. The potentialities of EUS are multiple, as it can also detect thickening and stenosis of the second duodenal part with intramural cyst and smooth stenosis of CBD. In the segmental form of solid variant, heterogeneous hyperechoic mass, enlargement of pancreatic head, with calcifications or pseudocysts and dilatation of main pancreatic duct, are frequently described.

It is generally accepted that with the use of EUS it is possible to localize the disease exactly and evaluate the surface involved, with the limitation being that EUS is not able to differentiate infiltration and inflammation. The possibility to obtain samples from suspicious lesions, by means of EUS-FNA, as well as the use of contrast-enhanced, makes EUS an ideal modality to differentiate pancreatic adenocarcinoma from PDP (especially solid variant), allowing a cytostatological diagnosis in nearly 90% of cases. However, insertion of EUS may be, sometimes, difficult or impossible due to duodenal stenosis and the accuracy of EUS is operator dependent [25]. On the other hand, results of EUS-guided fine-needle aspiration are variable depending upon the area of sampling. If the area sampled has abundant spindle cells, large numbers of giant cells or hyperplasia of Brunner’s glands, they may mimic neoplasia. This situation is particularly deceptive because the presence of giant cells and hyperplasia of Brunner’s glands are among the characteristic features of PDP. Likewise, an area with fibrosis does not rule out neoplasia, since it is common to find a desmoplastic reaction associated with the adenocarcinoma mimicking abnormal inflammatory changes (Table 1).
Differential diagnosis

The pancreatic-duodenal groove is a “theoretic” space between the pancreatic head and the duodenal wall. A number of small arteries, veins and lymphatic pass through this space. The most important vessel visible also on arterial phase of contrast enhanced imaging studies is the gastroduodenal artery and its branch pancreatic-duodenal artery that represents an important anatomical landmark [26]. Each process arising medially respect to the pancreatic-duodenal artery have a pancreatic origin, while those arising laterally have a duodenal or pancreatic-duodenal groove origin. Moreover, many important anatomical structures are present in the pancreatic-duodenal groove space such as CBD, main and accessory pancreatic ducts, major and minor papilla. This anatomical complexity account for many of the clinical and imaging features of PDP as well as for the differential diagnosis of this uncommon entity. Differential diagnosis, especially for solid variant, are mainly represented by pancreatic adenocarcinoma of the head of the pancreas, other pancreatic neoplasm, ampullary carcinomas, duodenal...
gastrointestinal stromal tumor or duodenal neuroendocrine tumors, as well as typical acute edematous pancreatitis involving the groove [5]. On the other hand, cystic dystrophy of the duodenum is a major mimic of duodenal adenocarcinoma, especially in patients who have circumferential wall thickening and enhancement, as in our case.

Although there are several radiological findings that may be used for preoperative diagnosis, differentiation of PDP (principally the solid variant, Groove Pancreatitis) from pancreatic head carcinoma may be, sometimes, impossible. Contrast-enhances CT and MRI are not reliable, especially when the tumour is scirrhous or has a high fibrous component. Pancreatic cancers, on the other hand, can also originate in the groove, making it difficult to distinguish them from solid variant of PDP. In 2010, Ishigami et al. [27] reported the utility of the portal venous phase in CT and MRI to distinguish PDP from pancreatic groove carcinoma, finding that the former more frequently presents with irregular focal enhancement in that phase. Subsequently Kalb et al. [28] achieved a diagnostic accuracy of 87.2% for PDP using three strict MRI criteria: focal thickening of the second duodenal portion, an abnormally increased enhancement of the second duodenal portion and cystic changes in the region of the accessory pancreatic duct. According to the authors, if these three criteria are met, ductal carcinoma of the head of pancreas can be ruled out, with a negative predictive value of 92.9%. Vascular invasion is an important sign for the differentiation of the two entities, especially invasion of the gastroduodenal artery and its branch, pancreatic-duodenal artery. This vessel appears infiltrated in the case of tumour and shifted to the left in the case of PDP. In evaluating CT images our attention, infact, was focused on this artery, which clearly appeared normal, only shifted, with regular contours and evident cleavage plan between the vessel and surrounding tissue (Figure 1). The presence of cystic lesions in the groove or duodenal wall, inflammatory thickening of the duodenal wall, and stenosis due to scarring of the duodenal lumen all indicates PDP.

**Current management**

A stepwise approach to treatment of PDP is feasible, effective and associated with an acceptable rate of complications. From a practical point of view, therapeutic options may be divided in conservative, medical and endoscopic, and surgery. Conservative measures including analgesics, pancreatic rest and abstinence from alcohol, are usually successful at treating the initial symptoms; sometimes enteral feeding is not possible in patients with duodenal stenosis who may require parenteral nutrition. Endoscopic treatment, including drainage of the pancreatic duct, dilatation of the stenosis and drainage of the cysts, is the mainstay of nonsurgical treatment and can be tailored to the clinical response.

Isayama and colleages [29] reported the treatment of solid variant of PDP by endoscopic stenting of the minor papilla, but the long-term clinical course remains obscure. Similarly, Casetti and colleages [30] showed poor results with endoscopic therapy. In their experience, all endoscopically treated patients eventually needed definitive therapy with pancreaticodudenoectomy. Endoscopic fenestration via cystoduodenostomy to drain the cysts appears effective in patients with cysts that are few in number and large. Disadvantages of endoscopic approach are the rate of symptoms recurrence and the possible complications due to the mobilization or obstruction of the prothesis. So medical and/or endoscopic treatment can be used as first choice in non-severe cases or “bridge” treatments prior to surgery with variable results. Infact, while first series reported that only small percentage of patients treated conservatively showed complete clinical responses [31], in more recent series complete response rate rise to almost 80% [32].

Surgery is the treatment of choice when symptoms do not improve or when the condition is too difficult to distinguish from pancreatic carcinoma. The preservation of the pylorus during pancreaticoduodenectomy is not always feasible because of extensive fibrosis of the pyloro-duodenal region. Whipple’s procedure for PDP (solid variant) may be more difficult in comparison to Whipple’s procedure for periampillary cancer, due to dense fibrosis in the pancreatoduodenal area.

Our patient has received a conservative treatment and has been discharged with a close follow up planned; smoking and alcohol ingestion has been discouraged. On the other hand, he has been carefully informed about the possibility of surgical intervention (pancreaticoduodenectomy) in case of unsuccessful medical management, future complications or suspicion of malignancy.

**Conclusion**

PDP (with its solid and cystic variant) is an uncommon and under-recognized form of recurrent or chronic pancreatitis that still represents a diagnostic challenge. Painful cystic lesions along the pancreatic groove in a male 40-60 years of age with a significant history of alcohol consumption and tobacco use should lead to consider the presence of this entity; before making a diagnosis of PDP, the possibility of malignancy should be carefully excluded.
Conflicts of Interest Statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors’ Contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Patient Consent

Informed consent was obtained from the patient for the publication of his information and imaging.

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