Disconnected pancreatic duct syndrome in patients with necrotizing pancreatitis

Petr Vanek, MD, Ondrej Urban, MD, PhD, Guru Trikudanathan, MD, Martin L. Freeman, MD

2nd Department of Internal Medicine – Gastroenterology and Geriatrics, University Hospital Olomouc, Faculty of Medicine, Palacky University, Olomouc, Czech Republic
Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, MN, USA

Abstract

In a subset of patients with acute necrotizing pancreatitis, segmental necrosis affecting the main pancreatic duct may result in a discontinuity between the left-sided pancreas and the duodenum. Such an interruption in the setting of a viable upstream portion of the gland can give rise to the disconnected pancreatic duct syndrome (DPDS). By maintaining its secretory function, the disconnected segment may lead to persistent external pancreatic fistulae, recurrent pancreatic fluid collections, and/or obstructive recurrent acute or chronic pancreatitis of the isolated parenchyma. There are currently no universally accepted guidelines for the diagnosis or treatment of DPDS, and because the condition is underrecognized, the diagnosis is often delayed. DPDS is associated with a prolonged disease course and poses a burden on patients’ quality of life as well as high health care resource utilization. The aim of our review is to summarize current knowledge, discuss diagnostic approaches, outline management options, and raise awareness of this challenging complication of necrotizing pancreatitis.

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Introduction

The Revised Atlanta Classification distinguishes mild, moderate, and severe forms of acute pancreatitis (AP) [1]. While the mild form is typically self-limiting and permits patients to leave the hospital within a few days, moderate and severe forms of AP are accompanied by local or systemic complications and constitute a complex disease requiring advanced medical and interventional care. The pathophysiological correlate of local complications of AP is primarily necrosis of pancreatic parenchyma or peripancreatic tissue (necrotizing pancreatitis [NP]), which occurs in approximately 15–20% of patients [1–6] (Fig. 1). In a subset of patients with NP, central necrosis affecting the main pancreatic duct (MPD) may create a discontinuity between the left-sided pancreas and the duodenum. Such an interruption in the setting of a viable upstream portion of the gland can give rise to the disconnected pancreatic duct syndrome (DPDS), which is generally regarded as a diagnostically and therapeutically challenging condition with variable clinical presentation [4].

Regarding local complications in AP, the literature has focused primarily on collections associated with pancreatic and/or peripancreatic necrosis. A number of expert recommendations and evidence-based guidelines have been based on multidisciplinary approaches using endoscopic, radiological, and surgical interventions [2,3,5–11]. However, DPDS has rarely been subjected to methodological analysis. In clinical practice, the syndrome is often overlooked and diagnosis delayed, although recognition of this entity may be crucially important for therapeutic decision-making. Patients with DPDS are more likely to require hybrid therapeutic interventions, reintervention, rescue surgery, or longer hospital stay [12–14].

The current paper presents an overview of the epidemiology, pathophysiology, clinical manifestations, and diagnostic strategies in patients with DPDS, as well as it outlines therapeutic options.

Definition

Disconnected duct is defined as circumferential interruption of the duct integrity, whereas a duct leak refers to its partial interruption [15]. It is important to differentiate these entities as they imply different management decisions. In a study comparing complete and partial disruptions, patients with complete MPD interruption had higher incidence of recurrent/refractory fluid collections or recurrence of pancreatitis after initial treatment, and required a higher frequency of surgical intervention [13]. A confusion in terminology and elemental concepts related to the syndrome may also be a hindrance to progress. The term disconnected pancreatic duct (DPD) describes an anatomical situation in which the ductal continuity between viable pancreatic tissue and the duodenum is interrupted (Fig. 2) without necessarily implying clinical manifestations. In contrast, DPDS emerges when the...
isolated pancreatic segment continues to have an exocrine output of digestive enzymes that is not drained into the bowel, with resulting consequences and symptoms (Fig. 3).

Nomenclature has been inconsistent. Although this clinical entity was originally described by Kozarek and colleagues as the disconnected pancreatic duct syndrome in 1996 [16], several authors have subsequently used terms such as disconnected pancreatic tail syndrome or disconnected left pancreatic remnant [14,17]. Nevertheless, the term DPDS is now widely accepted.

**Epidemiology**

The reported prevalence of DPDS in patients with NP is reported to range from 30 to 50% [12,13,18–21]. A prospective study recently confirmed the frequency of DPDS in patients with NP to be 46.2% [22]. However, results come mostly from relatively few heterogeneous cohorts, and interpreting them requires caution. Firstly, the necessity to perform advanced diagnostic modalities in order to meet the inclusion criteria within the studies, usually endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and/or perioperative pancreatography, may lead to an actual underestimation of the situation. DPDS often remains overlooked and underdiagnosed due to heterogeneity in clinical presentation, lack of well-defined diagnostic criteria, as well as inadequate recognition among clinicians [16,18,23]. Secondly, the general lack of clear distinction between DPDS, i.e., symptomatic DPD, and a clinically silent ductal disconnection or disruption in many studies may raise the question of whether the reported figures reflect the occurrence of true DPDS [24].

**Pathophysiology**

DPDS most often arises as a consequence of AP, and occasionally as a result of blunt abdominal trauma, pancreatic surgery, chronic pancreatitis, or pancreatic malignancy [25–27]. In the case of AP, DPD typically occurs in patients with severe and/or necrotizing forms. In a study by Neoptolemos and colleagues by using ERCP to evaluate the integrity of the MPD, some degree of MPD injury was demonstrated in 44% of patients with severe AP but none in patients with mild AP [18]. Bang and colleagues showed that the development of DPDS was associated with the presence of walled-off necrotic collections (WON) (Fig. 4), which were typically larger and multiple [12]. In that study DPDS was present in 84% of patients with WON. Most recently, Rana and colleagues found DPD (whether symptomatic or not) in 138 (77.1%) of 179 patients undergoing endoscopic ultrasound (EUS)-guided drainage [28].

Loss of ductal integrity occurs when pancreatic necrosis comprises ductal epithelial cells [13,18]. Such injuries to the MPD occur within the pancreatic head and the adjacent part of the neck and body (Fig. 5), most likely because of the susceptibility of these areas to ischemic necrosis due to the tenuous vascular supply [12]. In a retrospective series, the pancreatic neck was affected in 57.8%, followed by distal body–tail (23.1%) and mid body (19.2%) [29].

Ductal discontinuity results in extraductal and extrapancreatic leakage of pancreatic secretions into the surrounding tissues, leading to complications with heterogeneous clinical manifestations. The consequences of such pathological drainage virtually continue until it is interventio
cally redirected, the disconnected pancreatic segment is resected, or until it undergoes atrophy itself. In addition, scarring of the central end of the upstream duct may create a barrier to the outflow

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**Fig. 1.** Acute necrotizing pancreatitis within the body of the pancreas encompassing the main pancreatic duct – an illustration. Template courtesy of Dr. Rajeev Attam, Kaiser Permanente, CA, USA.

**Fig. 2.** Anatomical situation of a disconnected pancreatic duct following acute necrotizing pancreatitis – an illustration. Template courtesy of Dr. Rajeev Attam, Kaiser Permanente, CA, USA.

**Fig. 3.** Anatomical and pathophysiological situation of the disconnected pancreatic duct syndrome – an illustration. Template courtesy of Dr. Rajeev Attam, Kaiser Permanente, CA, USA.
of pancreatic juice from the distal parenchyma, which can result in a closed-space obstruction causing recurrent acute or chronic pancreatitis within the isolated segment.

**Clinical manifestation**

The clinical presentations of DPDS are highly diverse, including recurrent (peri-)pancreatic fluid collections (PFC), persistent external pancreatic fistula, pancreatic ascites, pleural effusions, and/or recurrent acute or chronic pancreatitis in the isolated upstream gland [4,12,29–34]. The timing of symptoms’ appearance can also be variable. DPDS may be identified during the initial presentation of NP, however, more typically recognized later on by its sequela [35].

The initial stage of acute NP is characterized by the systemic inflammatory response syndrome as a result of inflammatory mediators release, which contributes to the development of organ dysfunction [36]. At this point, features of DPDS are typically not investigated, and it is later in the disease course that the characteristics of DPDS begin to emerge. Such imprecision is less relevant in the initial treatment of severe AP as care is identical regardless of MPD integrity and directed toward fluid resuscitation, organ support, nutrition, and analgesia. Nevertheless, correct diagnosis of DPDS is often delayed by weeks to months [25].

DPDS is usually suspected in the presence of refractory peri-pancreatic collections [27]. Ductal disconnection in the setting of NP is distinct from other causes (trauma, chronic pancreatitis, surgery) because associated necrosis leads to the development of acute necrotic collections or WON, rather than a pseudocyst [12]. Patients with unrecognized DPDS at the time of successful initial endoscopic treatment of WON may present later with recurrence of collections. Another frequent presentation of DPDS is persistent external fistulas following percutaneous or surgical drainage or debridement. Pancreatic ascites or pleural effusions result from leakage of a pancreatic fistula toward adjacent organs [27]. In a recent prospective study, Maatman and colleagues reported that the most common presentations of patients requiring surgical management for DPDS were recurrent pseudocyst (40.9%) followed by pancreatic fistula (21.9%), pancreatic necrosis (21.9%), and recurrent AP (12.7%) [22].

It is worth noting that recurrent bouts of acute or chronic pancreatitis in the excluded parenchyma are infrequently described and possibly omitted, as recurring peripancreatic collections have been considered the major consequence. Recurrent acute and chronic pancreatitis usually present months to years after the necrosis has resolved [2], emphasizing the importance of long-term clinical follow-up of patients with NP. Additionally, pancreatic duct discontinuity may often be asymptomatic, with as yet unstudied prevalence.

**Diagnosis**

The diagnosis of DPDS is primarily based on imaging. Contrast-enhanced computed tomography (CECT), magnetic resonance (MR) imaging and/or MRCP, and EUS are currently the most applicable methods, in addition to the traditional technique of ERCP. In addition to avoidance of risk and less cost, these techniques allow imaging of the pancreas upstream of the disconnection, while ERCP only demonstrates termination of the downstream portion of the duct. Studies on the accuracy of various methods for detecting disconnected duct are scarce [24,37]. The criteria of radiologic studies that have been proven to confidently recognize DPD on imaging suggest that the following features are found [38]:

(a) an area of necrotic pancreas measuring 2 cm or greater (healing can occur with less extensive necrosis);
(b) the presence of viable pancreatic tissue upstream from the site of necrosis (Fig. 6);
(c) extravasation or total cut-off of contrast material injected into the MPD at pancreatography;
(d) pancreatic duct (possibly dilated) entering the collection at an approximately 90° angle (if visible).

In current clinical practice, pancreatic duct disruptions or disconnections are not vigorously sought in patients with acute NP, as the entire focus of initial management is elsewhere, even though the integrity of the MPD is an important contributor to long-term outcomes [12–14]. The diagnosis of DPDS may be concurrent with that of NP or may be evident often months–years after resolution of necrotic collections [39]. As mentioned, many patients with a disconnected MPD may remain completely asymptomatic.

Universally accepted recommendations or guidelines regarding diagnosing of DPDS are currently lacking. The revised Atlanta classification briefly mentions DPDS, or rather a disruption of the MPD in connection with necrotic collections or as a possible factor in the formation of pancreatic pseudocysts. In the section dedicated to WON, these guidelines state that demonstration of pancreatic ductal communication is
Abdominal CECT demonstrated the lowest sensitivity, pancreas duct in patients with moderate to severe AP during the index. Timmerhuis and colleagues performed a systematic review evaluating selected diagnostic methods for diagnosing disrupted or disconnected DPD could be traced in all, not a single original report described DPD features, and even though signs consistent with the diagnosis of DPDS has been diagnosed at a median duration of 1095 days) after symptoms onset in previous studies. The reason for delayed diagnosis could be explained by a lack of consensus in regard to the optimal approach.

Most recently, an international expert survey concerning diagnosis and treatment of pancreatic duct disruption or disconnection has identified a lack of consensus in regard to the optimal approach. No consensus was reached on whether routine imaging should be performed to evaluate MPD integrity in patients with NP. Nonetheless, the experts reached agreement in two important areas: MR/MRCP as the preferred diagnostic modality and endoscopic transmural drainage as the preferred intervention for patients with infected (peri-)pancreatic necrosis and MPD disruption or disconnection.

Contrast-enhanced computed tomography

CECT is widely available and remains the primary method for assessing the severity of AP and its complications in the majority of patients. CECT might be ideal for detection of DPD as well, although many patients with severe AP evolve inflammation and necrosis over time and the specific imaging findings for DPD may be apparent early in their initial hospitalization. Available data show that pertinent CECT findings of DPD become evident in most patients by 2 weeks after the initial insult. However, DPDS has been diagnosed at a median duration of 163 days (range 3–1095 days) after symptoms onset in previous studies. The reason for delayed diagnosis could be explained by a lack of awareness among treating physicians and a general unfamiliarity among radiologists. In a study by Tann and colleagues, CT images of 26 patients with surgically confirmed DPD were retrospectively reviewed for features of DPD, and even though signs consistent with the diagnosis of DPD could be traced in all, not a single original report described DPD.

Since CECT is employed in the majority of patients with NP, it is critical for treating physicians and radiologists to be aware of the entire spectrum of this entity. No imaging study would reveal the diagnosis if the evaluating physician was not familiar with DPDS and its implications.

Endoscopic retrograde cholangiopancreatography

The reference standard for establishing the diagnosis of MPD disruptions or disconnections has historically been ERCP. Pancreatogram may reveal a presence of contrast extravasation without filling of the MPD upstream or demonstrate complete MPD obstruction. In a study evaluating the diagnostic accuracy of ERCP in this indication, a sensitivity of 100% was demonstrated. Nonetheless, as an invasive procedure with a risk of complications, such as secondary infection of pancreatic necrosis, flare of pancreatitis, bleeding and perforation, its indications are subject to strict criteria. Furthermore, it may fail to show the upstream portion of the MPD and cannot differentiate between a high-grade stenosis and a disconnected duct.

Magnetic resonance imaging

While CECT remains the gold standard for assessing the severity of AP, MR has been shown to better characterize the content of collections and pancreatic ductal anatomy. Nonetheless, MR imaging might still not be routinely done at some institutions due to its cost, availability, and higher procedure time. The sensitivity of MR/MRCP to evaluate MPD integrity has been reported to be lower than the current reference standard ERCP, but with less risks of procedure-related complications. Secretin may be used to stimulate pancreatic secretion, facilitating the identification of the MPD and thus improving the diagnostic capabilities of MRCP. In a retrospective study by Gilliams and colleagues, secretin-enhanced magnetic resonance cholangiopancreatography (sMRCP) demonstrated sensitivity of 83.3% when compared with surgical confirmation of a disrupted pancreatic duct. Jang and colleagues compared sMRCP and MRCP with ERCP for detection of MPD disruptions in patients with moderate to severe AP, and reported a sensitivity of 92% and specificity of 100%, with an overall accuracy of 94%.

Fig. 6. Isolated distal pancreatic segment with duct dilatation (circled) in the setting of pancreatic body necrosis in a patient following endoscopic transmural drainage of WON; two indwelling DPSs in place (arrows). Courtesy of Dr. Rajeev Attam, Kaiser Permanente, CA, USA. WON – walled-off necrosis, DPS – double pigtail stent.

Fig. 7. Pancreatogram using sMRCP in a patient with DPDS diagnosed 5.5 years after index NP; isolated upstream pancreatic duct is circled. sMRCP – secretin-enhanced magnetic resonance cholangiopancreatography, DPDS – disconnected pancreatic duct syndrome, NP – necrotizing pancreatitis.
isolated MPD upstream. However, similar to ERCP, mechanical compression by a pancreatic collection or a focal stenosis may be difficult to differentiate from a duct disruption or disconnection even on MRCP, resulting in potentially false positive results [26,38].

**Endoscopic ultrasonography**

The role of EUS as a diagnostic modality in DPDS is unclear. EUS has proved to be useful for assessment of peripancreatic collections as well as for facilitating transmural drainage. Adequate visualization of the MPD and its continuity by EUS depends on the endoscopist’s expertise. In a prospective study, Bang and colleagues evaluated EUS in assessing MPD integrity in 21 patients during initial endoscopic transmural drainage of WON [49]. The findings were affirmed with histopathological confirmation after distal pancreatectomy or ERCP, and there was a 100% correlation between the initial EUS findings and final diagnosis of DPDS. Notably, the study included only patients with WON measuring >6 cm (duct disruption was present in 95%, n = 20), and 9 patients were excluded because of a suboptimal EUS characterization of the upstream duct. Thus, EUS could potentially aid in recognition of DPD prior or at the time of therapeutic endoscopic drainage [26,37,49].

**Amylase measurement**

Measurement of amylase or lipase levels in external drain output may be valuable for surgical or percutaneous drains, paracentesis for ascites, or thoracentesis for pleural effusions. MPD source is suspected when it contains >3-fold the normal serum amylase level [29,42,50]. A sensitivity of 100%, specificity of 50%, and an overall diagnostic accuracy of 65% for amylase measurements in drain fluid were found when compared with ERCP [51,52]. Nonetheless, this approach cannot distinguish between partial or complete pancreatic duct interruptions.

**Management**

Potential treatment strategies for DPDS include conservative treatment, endoscopic drainage, surgical drainage, distal pancreatectomy, prolonged percutaneous drainage, or combinations. According to a recent meta-analysis, the pooled success rates of strategies are high (>80%), with endoscopic transmural drainage reaching the highest value (92%) [53]. As there are no standardized guidelines available for DPDS, treatment currently remains at the judgment of treating clinicians [31]. In general, patients with DPDS are more likely than those without DPDS to need multiple advanced procedures and rescue surgeries [12–14]. While a detailed overview of therapeutic approaches in DPDS is beyond the scope of this review, some pertinent points specific to endoscopy and surgery are worth mentioning.

**Endoscopy**

Acute and recurrent collections associated with DPD are difficult to manage. Recurrent collections after endoscopic transmural drainage of WON have been reported in 7%–42% [43,54,55]. Previous studies reported a decrease in recurrence of PFCs when indwelling transmural plastic stents were either left in situ or exchanged after lumen-apposing metal stents so as to maintain patency of the internal fistula and divert pancreatic secretions into the gastrointestinal lumen [12,28,43,49,56,57]. Such an approach is currently favored, although the majority recommended removal of transmural stents, only after MPD integrity was evaluated MPD [40]. Nevertheless, such a strategy has been lately challenged by studies suggesting the incidence of symptomatic recurrences of peripancreatic collections after index drainage procedure was too low [58,59]. To support that viewpoint, in a randomized trial, Chavan and colleagues reported that deployment of plastic stents after metal stent removal did not reduce recurrence of peripancreatic collection in patients with DPD after WON [60]. Additionally, because the presence of pancreatic duct disruption or disconnection could influence the route of drainage and type of stent, evaluation of MPD integrity prior drainage may be considered, preferably with MR/MRCP if CECT cannot provide a definite answer [40]. The utility of transpapillary drainage in patients with DPD is markedly limited and is generally not recommended [3], the placement of a transpapillary pancreatic stent in order to reconnect the isolated pancreatic segment is often not feasible at first attempt due to the nature of the complete disconnection, which is in contrast with partial MPD disruptions that can be bridged with an endoprosthesis [3,26,61]. However, although data are conflicting, maintaining an internal pathway for pancreatic secretions once the necrotic cavity has resolved might be of value.

Leaving stents in cyst-enterostomy tracts has been widely recommended with the hope of reducing the risk of recurrent PFCs. However, it is not clear whether this strategy is effective at preventing scarring over of the central end of the upstream duct, which may cause recurrent acute or chronic pancreatitis in the excluded gland [2,12].

EUS-guided transmural drainage of recurrent fluid collections due to DPDS is now standard, with placement of hopefully permanent indwelling double pigtail stents. In the absence of a fluid collection, an EUS-guided pancreaticogastrostomy techniques have been described, which involve placement of an indwelling transmural stent into the upstream MPD to establish and maintain a duct-enteric fistula [62,63] (Fig. 8). Another approach in the setting of a pancreaticocutaneous fistula is to combine endoscopic and radiointerventional percutaneous rendezvous techniques to internalize the fistula tract back into the stomach or duodenum [34].

**Surgery**

Despite the continual evolution of advanced endotherapy, surgery is still needed in a number of patients with DPDS. Surgery results in a high success rate and eventually provides a definite solution. Surgical treatment of persistent DPDS may involve resection of the upstream gland, with or without pancreatic islet cell autotransplantation to reduce the risk of diabetes mellitus (DM) [64] or, if the upstream duct is of adequate size, Roux-en-Y pancreaticojjunostomy preserving pancreatic function and physiological drainage of pancreatic secretions [2,65]. In a prospective study by Maatman and colleagues, 68% (202/299) DPDS patients required operative intervention specifically for symptoms...
caused by DPDS (17.3% had failed endoscopic attempts before surgery) with resolution of symptoms reported in 89% [22]. The most common surgery performed was internal drainage (46.8%) followed by resection procedures (38.4%), whereas remaining 14.8% patients underwent open necrosectomy. Nevertheless, post-operative morbidity is considerably high, and distal pancreatectomy has the highest risk of long-term endocrine and exocrine insufficiency [53]. An advantage of endoscopic treatment is that it does not prevent subsequent surgery in case of technical or clinical failure.

Future challenges

DPDS requires attention both in the acute and chronic phases of NP. However, data addressing its natural history are scarce, likely due to its underdiagnosis, misdiagnosis, as well as inadequate follow-up of patients who do not develop symptomatic DPDS after hospital discharge. It is still unclear how many patients with disconnected duct remain asymptomatic or resolve their syndrome without intervention, rendering a generally interventional approach excessive. On the other hand, early diagnosis of DP may reduce treatment delay in patients who would otherwise linger through a prolonged disease course [53]. Optimal outcomes can be expected in most patients with DPDS using a combined multimodality approach consisting of endoscopy and timely surgery if needed [26], provided the diagnosis is recognized.

Unrecognized and untreated DP may result in pancreatic atrophy and chronic pancreatitis, with resultant exocrine or endocrine insufficiency [57]. Exocrine insufficiency may be seen in 0–14% patients with DP, while new-onset DM may be seen in 16–52% [12,25,43,57]. Most recently, Thiruvengadam and colleagues reported in their retrospective study that pancreatitis of the disconnected pancreas occurred in 16% of DPDS patients, and it was associated with higher rates of new-onset DM after pancreatitis (defined as DM occurring >3 months after NP) when compared with patients with other manifestations of DPDS and patients without DPDS [66]. In addition, there is an intuitive conclusion that the larger the volume of the disconnected upstream segment, i.e., proximal disconnection, the greater the risk of DM, as it was recently supported by Basha and colleagues [59]. The uncertainties revolve around the question of whether drainage or procurement of upstream gland before atrophy sets in would be of benefit.

Large-scale studies of unselected cohorts of patients with NP, specifically seeking out DP, are needed to determine the exact incidence and prevalence of this entity to develop optimal algorithms for early diagnosis as well as effective treatment strategies.

Conclusion

DPDS is an underrecognized complication of NP, although it may become a dominant long-term challenge in this patient population. DP is heterogeneous and diagnosis often delayed, with the most common reason for late diagnosis being the lack of awareness among treating physicians. During the diagnostic delay, patients suspected of DPDS should include those with nonresolving physicians. During the diagnostic delay, patients suspected of DPDS were noted as being considerably high, and distal pancreatectomy has the highest risk of long-term endocrine and exocrine insufficiency [53]. An advantage of endoscopic treatment is that it does not prevent subsequent surgery in case of technical or clinical failure.

CRediT authorship contribution statement

P Vanek – Conceptualization, Review of literature, Original draft preparation; O Urban – Critical revision of manuscript; G Trikudanathan – Review of literature, Critical revision of manuscript; ML Freeman – Final revision and editing of manuscript.

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