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Endoscopic treatment of refractory external pancreatic fistulae with disconnected pancreatic duct syndrome

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ABSTRACT

Background: External pancreatic fistulae (EPF) developing in setting of disconnected pancreatic duct syndrome (DPDS) are associated with significant morbidity and surgery is the only effective treatment.
Aim: To describe safety and efficacy of various endoscopic including endoscopic ultrasound (EUS) guided drainage techniques for resolving EPF in DPDS.
Methods: Retrospective analysis of data base of 18 patients (15 males; mean age: 37.6 ± 7.1years) with EPF and DPDS who were treated with various endoscopic techniques including EUS guided transmural drainage.
Results: EPF developed post percutaneous drainage (PCD) (n = 15) or post-surgical necrosectomy (n = 3) of acute necrotic collections. All patients had refractory EPF with daily output of >50 ml/day with mean duration being 19.2 ± 6.1 weeks. One patient had failed surgical fistulo-jejunostomy. Various endoscopic techniques used were: transmural placement of pigtail stent through gastric opening of trans-gastric PCD (n = 5), EUS guided transmural puncture of fluid collection created by clamping PCD (n = 5) or by instillation of water though PCD (n = 3), direct EUS-guided puncture of fistula tract (n = 1) and EUS guided pancreaticogastrostomy (n = 4). EPF healed in 17/18 (94%) patients within 5–21 days and there has been no recurrence over follow up of 16.7 ± 12.8 weeks. Asymptomatic spontaneous external migration of stents was observed in 5/18 (29.4%) patients.
Conclusion: Management of refractory EPFs in setting of DPDS is challenging. In our experience, combination of various endoscopic techniques including EUS guided transmural drainage appears to be safe and effective treatment modality for treating these complex EPF's. However, further studies to identify patient selection and best treatment approaches are needed.

Introduction

Pancreatic duct (PD) disruption can lead on to formation of external or internal pancreatic fistulae [1,2]. Endoscopic transpapillary pancreatic duct stent or nasopancreatic drain placement is an effective minimally invasive alternative to surgery for management of external pancreatic fistulae (EPF) [1–5]. Transpapillary endoprosthesis facilitate healing of EPF by obliterating transpapillary pressure gradient and facilitating drainage of pancreatic juice through the papilla [6]. Endoscopic drainage is usually successful in patients with partial PD disruption that has been bridged by endoprosthesis. It is not so effective in patients with partial PD disruption that has not been bridged or in patients with complete PD disruption [7]. The EPF closure has been reported in 70–100% of patients with partial PD disruption that has been bridged whereas the closure rates are only 20–33% in patients with complete PD disruption [1–5,7].

Complete PD disruption with presence of significant amount of functional pancreas upstream to disruption leads on to disconnected pancreatic duct syndrome (DPDS) [8]. EPF in setting of DPDS usually does not respond to conservative therapy as disconnected functional pancreas continue to pour pancreatic juice through low resistance path of EPF. Moreover, endoscopic transpapillary drainage is not effective in this setting as disruption cannot be bridged [7,8]. The therapeutic options available in this setting are:

1. Prolonged percutaneous drainage (PCD) with other conservative treatment strategies like subcutaneous octreotide, parenteral nutrition or nasojejunal feeding. However, these conservative treatment strategies are not effective. Also, prolonged PCD is

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associated with various complications like inconvenience, poor quality of life, leakage of protein rich pancreatic juice through skin site with consequent malnutrition and risk of infection.
2. Surgery (usually distal pancreatectomy), although effective, is associated with significant morbidity and mortality because of associated adhesions as well as presence of venous collaterals because of commonly associated splenic vein thrombosis [7–9]. The development of pancreatic endocrine as well as exocrine insufficiency post-surgery is also a concern.

Patients with walled off necrosis (WON) and associated DPDS are best managed by leaving transmural plastic stents in situ for an indefinite period following successful outcome of endoscopic transmural drainage [10–12]. This strategy has been shown to be a safe and effective strategy of providing enteral drainage to disconnected functional pancreas and thus prevent recurrence of pancreatic fluid collections (PFC) [10–12]. Endoscopic transmural drainage combined with PCD in patients with WON and associated DPDS also prevents formation of EPF by providing enteral drainage to pancreatic secretions [13]. EPF's associated with persisting PFC's and associated DPDS have also been successfully treated with endoscopic ultrasound (EUS) guided transmural drainage of co-existing PFC [14,15].

However, refractory EPF with DPDS in absence of co-existing PFC usually necessitates surgery as absence of PFC precludes any endoscopic attempt to provide enteral drainage to disconnected pancreas. There have been few novel minimally invasive endoscopic attempts to treat these refractory EPF but experience is limited [8,16]. In this study, we present the safety and efficacy of various endoscopic techniques including EUS guided transmural drainage for treating persistent EPF in patients with associated DPDS.

Patients and methods

Patients

The database of patients with acute necrotising pancreatitis (ANP) treated in our unit over last five years was retrospectively searched to retrieve data of patients with EPF and DPDS without any co-existent PFC who were treated with an attempted endoscopic/EUS guided transmural drainage. All patients had been earlier diagnosed with ANP based on revised Atlanta classification and had developed EPF because of percutaneous or surgical drainage of acute necrotic collection [17].

The included patients had persistent drain output (>50 mL/day) of amylase rich fluid for >6 weeks. The DPDS was defined as either a cut off or blowout of main PD with diffuse extravasation of contrast along with inability to demonstrate upstream PD on pancreatogram obtained during endoscopic retrograde pancreatography (ERP). No patient had PFC detected on cross sectional imaging. An informed consent was obtained from patients before the endoscopic procedure.

Methods

Initially, all these patients underwent gastroscopy to identify inadvertent trans-gastric puncture of acute necrotic collections by PCD catheter. If PCD catheter was seen in stomach, the gastroscope was replaced with a duodenoscope and site of exit of PCD from stomach into collection was identified and cannulated. Thereafter, a 0.025" guide wire (VisiGlide Guide wire; Olympus Corp, Japan) was coiled around the tip of PCD catheter (Group A). This technique of internalising EPF has been described by us earlier [16]. After securing the guide wire, PCD catheter was removed and 7Fr, 3 or 5 cm, double pigtail plastic stent was placed through the stomach thereby internalising EPF (Fig. 1a–c). If the PCD catheter was not visualised in stomach on gastroscopy, alternative EUS guided techniques as mentioned below were used.

EUS guided techniques

Initially an attempt was made to create a PFC by clamping PCD catheter and newly formed PFC was treated by EUS guided transmural drainage (Group B). However, if clamping of PCD catheter led on to seepage of pancreatic juice from the cutaneous site, the catheter was opened and alternative techniques in step wise manner, as mentioned below, were used.

As a first step, 100–300 ml of sterile distilled water was injected through the PCD catheter to create artificial collection of water. If peri-gastroduodenal water collection could be created, EUS guided transmural drainage of newly created water collection was done (group C). However, if collection could not be created, either EUS guided direct transmural puncture of fistula tract (with pigtail tip visualised on EUS) (Group D1) or of upstream disconnected pancreatic duct (if > 4 mm in diameter) (Group D2) was performed. All EUS guided procedures were performed under conscious sedation with analgesia using intravenous midazolam and tramadol. The EUS guided procedures were done using linear echoendoscope (EG-3870 UTK linear echoendoscope, Pentax Inc., Tokyo, Japan or UCT180 linear echoendoscope, Olympus Optical Co., Ltd., Tokyo, Japan). All punctures were made by using a 19G needle and a 0.025" guide wire (VisiGlide Guide wire; Olympus Corp, Japan) was used.

EUS guided transmural drainage of newly created PFC following withdrawal of PCD catheter (Fig. 2a–c) (group B)

The PCD catheter was clamped for 48 h and thereafter EUS examination was done with linear scanning echoendoscope to localise newly created PFC. The patients received pre-procedure intravenous ciprofloxacin. Once localised, the collection was punctured using 19G needle and after placing 0.025" guide wire (VisiGlide Guide wire; Olympus Corp, Japan) the transmural tract was dilated with 6 Fr cystotome (Cysto Gastro Set; Endoflex, GmbH, Voerde, Germany). If PFC was more than 4 cm in diameter, the transmural tract was further dilated with 4 mm diameter balloon (4 cm length; Hurricane; Boston Scientific, Marlborough, MA, USA) and one or two 7 Fr, 3 or 5 cm double pigtail or single 10Fr, 3 or 5 cm double pigtail plastic stents were placed. If PFC was ≤4 cm in diameter, no further dilatation of transmural tract was done and 7Fr, 3 or 5 cm, double pigtail plastic stent was placed.

EUS guided transmural drainage of artificial water collection formed after instillation of distilled sterile water (Fig. 3a–c) (Group C).

Under EUS guidance, 100–300 ml of distilled water was injected through PCD catheter to create an artificial collection of water. Once a water collection was visible on EUS, transmural drainage, as described earlier, was performed.

EUS guided transmural drainage of fistula tract (Fig. 4a–c) (group D1)

Patients in whom above mentioned techniques failed to create a PFC and pigtail catheter tip was closely abutting gastroduodenal lumen, direct puncture of fistulous tract was done under EUS as well as fluoroscopic guidance. The transmural tract was dilated with 6Fr cystotome and a single 7Fr, 3 or 5 cm, double pigtail plastic stent was placed.

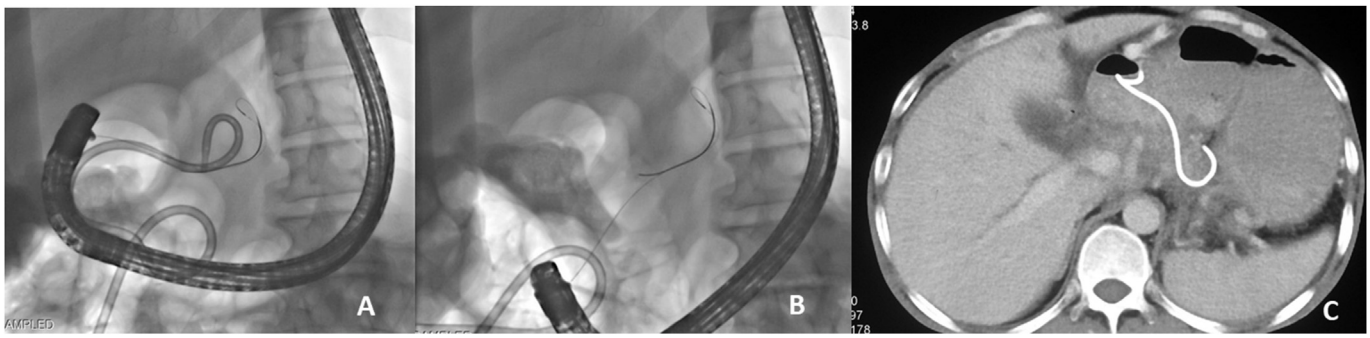

Fig. 1. A: The transgastric catheter site cannulated alongside the PCD and the guide wire manipulated into the fistula tract. **B**: The PCD removed and guide wire secured in the fistula tract. **C**: CT: The transmural stent in situ.

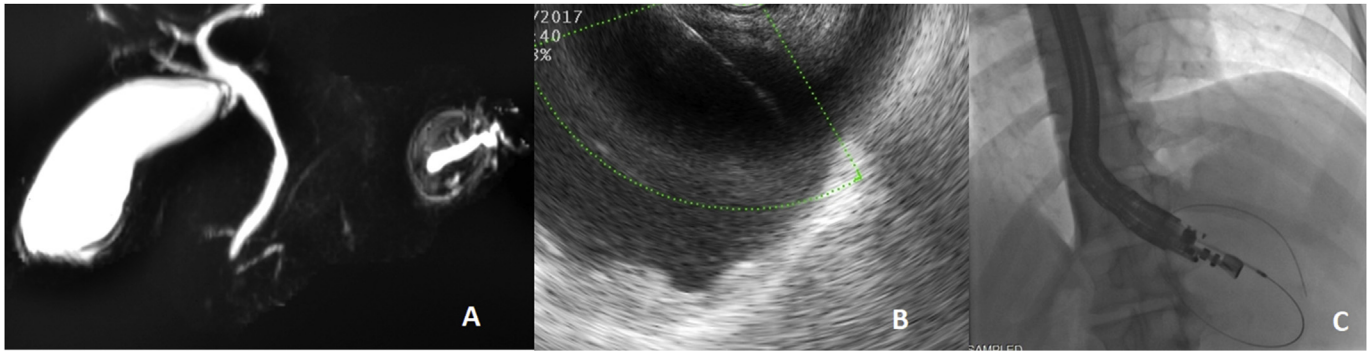

Fig. 2. A: MRCP: Disconnected pancreatic duct in patient with EPF. **B**: Fluid collection formed after clamping PCD for 48 h. **C**: EUS guided transmural drainage: Guide wire in situ with tract being dilated with cystotome.

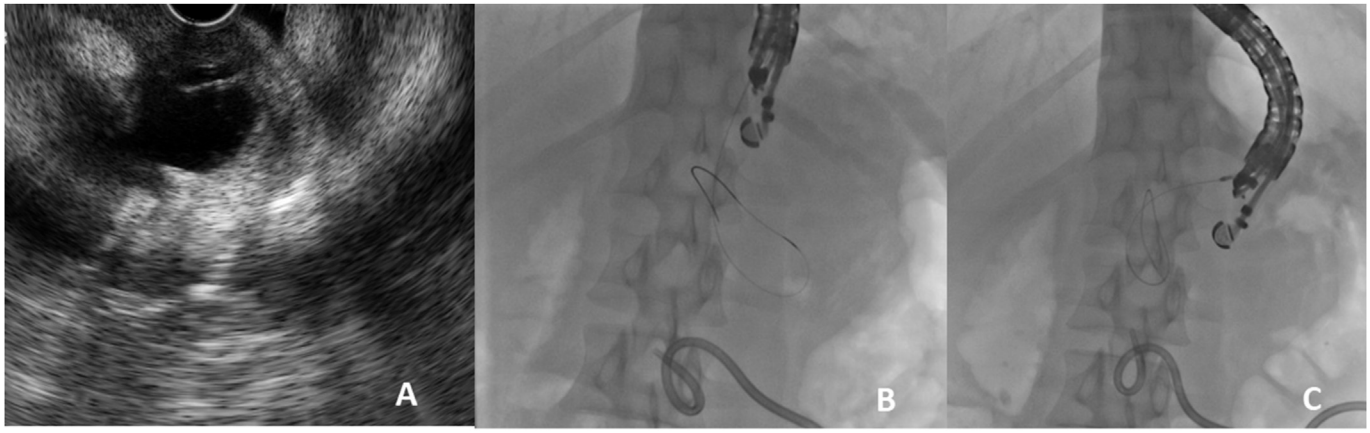

Fig. 3. A: Fluid collection created with instillation of distilled water through the PCD. **B**: EUS guided transmural drainage: Guide wire in situ. **C**: EUS guided transmural drainage: transmural tract being dilated with cystotome.

EUS guided PD drainage of disconnected pancreas (group D2)

Patients in whom above mentioned techniques failed to create PFC, tip of pigtail catheter was not adjacent to gastroduodenal lumen and diameter of PD of disconnected pancreas was more than 4 mm, EUS guided direct drainage of PD was done. Briefly, using a linear echoendoscope, dilated PD was localised in upstream disconnected pancreas and punctured using a 19G needle. Thereafter 0.025" guide wire (VisiGlide Guide wire; Olympus Corp, Japan) was pushed and coiled till the tail end of disconnected pancreas. The transmural tract was dilated with 6 Fr cystotome (Cysto Gastro Set; Endoflex, GmbH, Voerde, Germany) followed by placement of 5 Fr plastic stent.

Follow up

Treatment Success: Defined as successful closure of EPF with removal of PCD catheter and complete cessation of drainage of pancreatic juice from cutaneous site without resorting to surgery.

Treatment Failure: Need for surgery either for any complication of EUS guided drainage procedure or non-resolution of EPF.

After endoscopic procedure, patients were discharged and

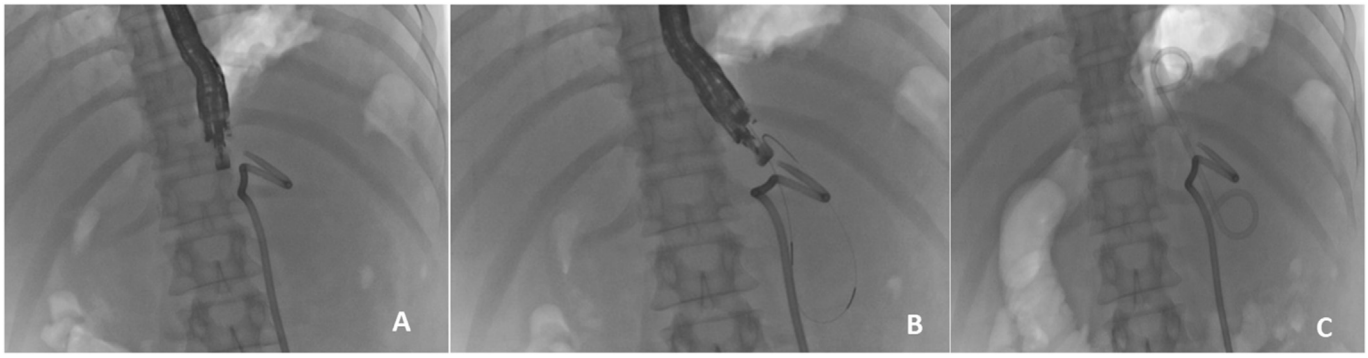

Fig. 4. **A**: EUS scope positioned close to tip of PCD. **B**: EUS guided transmural puncture close to tip of pigtail with guide wire in situ. **C**: Transmural stent placed. PCD is also noted.

followed up clinically as well as by cross sectional imaging. The patients were followed at weekly interval in outpatient department till fistula output decreased to less than 10 ml/day for three consecutive days. Following this, computed tomography was performed to confirm absence of PFC and thereafter PCD catheter was removed. The transmural stent/stents were left for an indefinite period in patients in group A, B, C and D1. The transmural stent was removed in patients in group D2 after 6 months and matured transmural tract was re-cannulated with placement of a new plastic stent. All these patients were followed up clinically at monthly intervals for six months. Patients not reporting to outpatient department for contacted telephonically for recurrence of EPF or development of new symptoms. After 6 months, asymptomatic patients were followed up at 6 monthly interval with an abdominal x ray to confirm presence of transmural stent in situ.

Results

Over a period of 5 years, 18 patients (fifteen males; mean age: 37.6 ± 7.1years) with refractory EPF and DPDS were studied. All patients had persistent drain output (>50 mL/day) of amylase rich fluid for >6 weeks after percutaneous (n = 15) or surgical drainage (n = 3) of PFC. The etiology of ANP was alcohol in 14 and gall stone diseases in 4 patients. The mean duration of EPF was 19.2 ± 6.1 weeks. One patient had recurrence of fistula after failed surgical fistulo-jejunostomy.

All patients underwent successful endoscopic internalisation of EPF by using various endoscopic or EUS guided internalisation techniques. Five patients underwent endoscopic guided cannulation of gastric opening of trans-gastric PCD and subsequent placement of 7 Fr double pigtail stent/stents (Group A).

The various EUS guided techniques used in remaining patients were as follows:

EUS guided transmural puncture of PFC created by clamping PCD (group B): Five patients
EUS guided transmural puncture of artificial collection of water created by injection of distilled water (Group C): Three patients
Direct EUS-guided puncture of fistula tract (group D1): One patient
EUS guided pancreaticogastrostomy (Group D2): Four patients

All punctures were done through the stomach and following stents were placed:

A. Endoscopic guided cannulation of gastric opening of trans-gastric PCD (group A): single 7 Fr 5 cm double pigtail stent in 2 patients; two 7 Fr 5 cm double pigtail stent in one patient, and single 7Fr 3 cm double pigtail stent in two patients.
B. EUS guided transmural puncture of PFC created by clamping PCD (group B): single 10 Fr 3 cm double pigtail stent in 2 patients, two 7Fr 5 cm double pigtail stent in one patient, single 7 Fr 5 cm double pigtail stent in one patient and single 7 Fr 3 cm double pigtail stent in one patient respectively
C. EUS guided transmural puncture of artificial water collection created by injection of distilled water (Group C): single 7 Fr 5 cm double pigtail stent in all three patients
D. Direct EUS-guided puncture of the fistula tract (Group D1): single 7 Fr 5 cm double pigtail stent in one patient
E. EUS guided pancreaticogastrostomy (Group D2): 5 Fr 7 cm double pigtail stent in one patient, 5 Fr 5 cm double pigtail stent in one patient, 5 Fr 9 cm straight stent in two patients

Complications: Patient who underwent direct EUS guided puncture of fistula tract (Group D1) had transient abdominal pain that subsided with intravenous analgesics and bowel rest for 24 h. No other complications of endoscopic procedures were observed.

Outcome after endoscopic intervention

Following, transmural stent placement, EPF healed in 17/18 (94.4%) patients within 5–21 days. One patient had two EPF's and one fistula healed 17 days after the endoscopic intervention (group B). However, second fistula persisted and therefore, patient underwent successful surgical fistulo-jejunostomy. There has been no recurrence of EPF or any symptoms in any of these 17 successfully treated patients over follow up of 16.7 ± 12.8 weeks. Asymptomatic spontaneous external migration of transmural stents was observed in 5/18 (29.4%) patients. The transmural stents migrated externally in 2 patients at 3 months (both straight pancreaticogastrostomy stents; Group D2), 7 Fr 5 cm double pigtail stent in 1/5 patients who underwent endoscopic guided cannulation of the gastric opening of the trans-gastric PCD (3 months; Group A), 7 Fr 5 cm double pigtail stent in 1/5 patients who underwent EUS guided transmural puncture of PFC created by clamping PCD catheter (8 months; Group B), and 7Fr 5 cm double pigtail stent in 1/3 patients who underwent EUS guided transmural puncture of water collection created by injection of distilled water (10 months; Group C).

Discussion

Because of limited efficacy of endoscopic transpapillary drainage for EPF in setting of DPDS, surgery is the only effective therapeutic option. However, availability of therapeutic EUS has led on to exploration of various endoscopic techniques to treat these

complex EPF's non-surgically [8,15,16,18]. Arvanitakis et al. treated 11 patients with refractory EPF with a combination of endoscopic and EUS guided techniques [15]. EUS guided transmural drainage of co-existent PFC or artificial PFC created by injection of water or contrast medium through PCD was done in 5 patients whereas transmural drainage between fistula path and gastrointestinal (GI) tract was done in 5 patients. EUS-guided pancreatico-duodenostomy was done in one patient. Following endoscopic therapy, EPF healed in all except one patient who was treated surgically. During a median follow-up of 18 months, three patients had recurrence of EPF and two had recurrence of PFC's that were managed endoscopically.

Irani et al. reported novel endoscopic and percutaneous rendezvous techniques to completely resolve EPFs in 15 patients with DPDS [8]. Outside to inside rendezvous technique was used in 10 patients where existing PCD was used to puncture into the stomach/duodenum by using Transjugular Intra-hepatic Porto-systemic shunt (TIPS) needle and thereafter through the needle guide wire was manipulated into stomach and captured endoscopically. Subsequently, transmural tract was dilated and stents placed. In inside to outside rendezvous technique, EUS was used to puncture into fistula tract and thereafter guide wire was grasped by interventional radiologist. The tract was dilated over guide wire and transmural stents placed. The EPF closed in all patients within a medium time of 7 days with no recurrence of EPF in any patient at a median follow-up period of 25 months.

EUS guided transmural drainage of dilated PD, either into stomach (pancreaticogastrostomy) or duodenal bulb (pancreaticoduodenostomy), has also been reported to heal refractory EPF in setting of DPDS [8,18–21]. EUS guided PD drainage in setting of EPF is very challenging and associated with increased risk of technical failure as well as complications. This difficulty is because of the small diameter of PD as it is decompressed by EPF.

In this study, we reported combination of various endoscopic techniques for internalising EPF in setting of DPDS. In patients with indwelling PCD catheter traversing through stomach, we internalised EPF by cannulating and subsequent placement of transmural stent through the site of exit of PCD catheter from the stomach into collection. We used this technique successfully in five patients with no complications. In patients with EPF and PCD catheter not traversing the stomach, we first clamped PCD catheter for 48 h. In 5/13 patients, a small fluid collection was created adjacent to stomach and was punctured under EUS guidance followed by placement of transmural stents. The EPF healed in all these 5 patients and no major complication was encountered. In remaining 8 patients, pancreatic juice started seeping around PCD catheter and no fluid collection was formed.

In these patients, 100–300 ml of sterile distilled water was injected through PCD catheter under EUS and fluoroscopic guidance to create an artificial water collection. In three patients, a small collection of water was created and endoscopic transmural drainage of this artificial water collection led on to healing of EPF. In remaining 5 patients, there was diffuse intra-abdominal leakage of fluid injected. Four of these 5 patients had upstream PD > 4 mm in diameter and were successfully treated with endoscopic transmural drainage of PD. One patient with PD < 4 mm in diameter underwent successful EUS guided direct puncture of fistula tract. Our study suggests that patients with EPF associated with DPDS can be treated with minimally invasive endoscopic interventions. Various endoscopic intervention options including EUS guided interventions are available and the choice of intervention depends upon presence of co-existent pancreatic fluid collection, main pancreatic duct diameter and the transabdominal route of PCD catheter.

Asymptomatic spontaneous external migration of transmural stents was observed in 5 (29.4%) patients and was seen more commonly in patients who underwent EUS guided pancreaticogastrostomy. Spontaneous migration of permanent indwelling transmural stents has been described in up to one third of patients and can lead on to recurrence of symptoms/fluid collections [12]. However, none of our patients with spontaneous migration of stents had recurrence of EPF. Previous studies have also demonstrated that spontaneous migration does not lead to recurrence of PFC in all patients [12,18,22,23]. Early migration of stents, ductal disruption in pancreatic head as well as absence of diabetes, steatorrhea, and pancreatic atrophy seems to increase risk of recurrent PFC/symptoms following migration of transmural stents in patients with DPDS [22].

Small sample size, being a single centre study and retrospective study design are important limitations of the current study. Also, patients studied were highly selected group who were managed by using different endoscopic techniques with no comparative group at a highly specialized centre with extensive experience in pancreatic endotherapy and patients were followed up for a relatively short mean period of 16.7 weeks.

In conclusion, management of refractory EPFs in the setting of DPDS is challenging and difficult. In our experience, combination of various endoscopic techniques including EUS guided transmural drainage appears to be safe and effective minimally invasive treatment modality for treating these complex EPF's. However, further studies to identify patient selection and best treatment approaches are needed.

Author contributions

1. Surinder Singh Rana: Design, Collection and interpretation of data, drafting of manuscript.
2. Ravi Sharma: Collection and interpretation of data.
3. Rajesh Gupta: Collection and interpretation of data.

Conflicts of interest

1. Surinder Singh Rana: None.
2. Ravi Sharma: None.
3. Rajesh Gupta: None.

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