Pancreaticopleural Fistula: A Review
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ABSTRACT
Pancreaticopleural fistula is a rare complication of chronic pancreatitis consequent to posterior disruption of the pancreatic duct. The fistulous track ascends into the pleural cavity and gives rise to large volumes of pleural fluid. Pancreaticopleural fistula thus poses a diagnostic problem since the source of pleural fluid is extrathoracic. To further complicate the matter, abdominal pain is seldom the presenting or significant feature. The pleural effusion is typically rapidly accumulating, recurrent and exudative in nature. Pleural fluid amylase in the correct clinical setting virtually clinches the diagnosis. Magnetic Resonance Cholangiopancreatography, Endoscopic Retrograde Cholangiopancreatography and Computed Tomography may delineate the fistula and thus aid in diagnosis. Endoscopic Retrograde Cholangiopancreatography has emerged both as a diagnostic as well as therapeutic modality in select patients of pancreaticopleural fistula while Magnetic Resonance Cholangiopancreatography is the radiological investigation of choice. Besides delineating the ductal anatomy, Magnetic Resonance Cholangiopancreatography can help stratify patients for appropriate management. A near normal or mildly dilated pancreatic duct responds well to chest drainage with octreotide while endoscopic stent placement benefits patients with duct disruption located in head or body of pancreas. Failure of medical or endoscopic therapy calls in for surgical intervention. Besides, a primary surgical management may be tried in patients with complete ductal obstruction, ductal disruption in tail or ductal obstruction proximal to fistula site.

INTRODUCTION
Pleural effusion in acute pancreatitis is chemically induced or sympathetic in nature [1]. It plagues 3 to 17% of patients [1]. Its presence is a marker of prognosis [2]. However, the pleural effusion is self-limiting [1]. On the contrary, pleural effusion in chronic pancreatitis is a rarity [3] and may be due to pancreaticopleural fistula [3] (constitutes 1% of cases of pleural effusion [4]). Digestive property inherent to pancreatic succus can dissect through the fascial planes and may form a communication either anteriorly (pancreaticoperitoneal fistula) [1] or posteriorly [5] into retroperitoneum. The retroperitoneal fluid collection then ascends superiorly and dissects into the pleural cavity (pancreaticopleural fistula) [5, 6]. This fistulous track thus feeds the pleural space with amylase rich secretions. The PPF related pleural effusion is typically refractory to drainage and has a tendency to accumulate rapidly [1, 2, 4]. Chest symptoms predominate [1-4]: hence diagnosis is a challenge [7, 8]. Detection of high amylase levels in pleural effusion is a characteristic finding [9]. Sensitivity of radiological investigations is variable [10]. Computed Tomography is thus best reserved for detection of pleural effusion [1, 4] and associated changes in pancreatic parenchyma [2, 7, 8]. Both Endoscopic Retrograde Cholangiopancreatography and Magnetic Resonance Cholangiopancreatography help visualise ductal anatomy [2, 3]. While the former has the added advantage of being therapeutic [2, 10], the latter may help visualise the duct beyond the site of obstruction [10, 11]. Besides, a management approach has also been suggested on the basis of ductal anatomy as depicted on MRCP [12]. Medical therapy in the form of thoracocentesis and or tube thoracostomy with somatostatin analogues is the initial management [1, 4]. Patients who benefit the most are the ones with minimal ductal changes [12]. A ductal disruption present in the head or body of pancreas can be bridged using a stent [12]. Further, a stent placed close to the site of disruption atleast relieves ductal pressure due to chronic pancreatitis mediated strictures [Dhebri]. Surgery, in the current era, is usually resorted to when medical or endoscopic therapy fails [1, 4, 12]. However, primary surgery has its own benefits like lesser complications and shorter recovery period [7]. Moreover, complete ductal obstruction or obstruction proximal to fistula site or a leak in the tail are best managed by a primary surgical intervention [12].

EPIDEMIOLOGY
Recognition of pancreaticopleural fistula (PPF) as a distinct clinical entity dates back to late 1960s [13]. The classic description of a patient suffering from PPF includes

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Abbreviations PPF Pancreaticopleural fistula
CP Chronic pancreatitis
CT Computed Tomography
ERCP Endoscopic Retrograde Cholangiopancreatography
MRCP Magnetic Resonance Cholangiopancreatography
TPN Total parenteral nutrition

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a middle-aged, chronic alcoholic male with a history of breathlessness [14]. Males constitute four-fifths of the cases [15]. PPF mediated pleural effusion presents with dyspnea in 65-76% of cases [10, 16]. Cough (27%), chest pain (23%) and fever are seen with a lesser frequency [10, 15]. Abdominal pain may be seen in 29% of patients [10, 15]. Since chest symptoms predominate, diagnosis is usually delayed. A delay of 12-49 days has been described (Dhebri). Characteristically the pleural effusion in PPF has a tendency to recur [1, 2, 4]. Concomitant involvement of other body cavities may also occur. Pancreatic ascites with pleural effusion is seen 20% of times while 4% of patients have both pancreatic pleural as well as pericardial effusion [14].

PPF is seen in 0.4% of patients presenting with pancreatitis [1, 17]. CP related to alcohol abuse (67%) is the most common causative factor in adults [15] while biliary duct obstruction constitutes the major etiological factor in children [18]. Other causes giving rise to PPF include gall stones, abdominal trauma, and pancreatic duct anomalies [7]. Trauma contributes 0.5% of cases [8]. PPF is seen in 4.5% of patients with pancreatic pseudocysts [1, 17]. Conversely, a pseudocyst is found in 43-79% cases of PPF [8, 16, 19]. Development of PPF usually results from posterior leakage [5] of an incompletely formed pseudocyst or rupture of a mature one [2, 7]. The fistulous track traverses across aortic or esophageal hiatus [12, 18] or rarely via transdiaphragmatic route [1] and empties into either (76% times on left [7, 14] while right sided in 19% patients [1]) or both pleural spaces (14% of cases) [1]. Alternatively, a ruptured mediastinal pseudocyst also results in formation of PPF [7, 8, 20].

**DIAGNOSIS**

Diagnosis of PPF is challenging [7, 8] and requires high index of suspicion [1, 2, 4]. PPF related pleural effusion needs to be differentiated from the reactive effusion that occurs in acute pancreatitis [15, 21]. The latter is self-limiting [1] and has normal amylase and albumin content [15, 22]. The former however, rapidly accumulates and is refractory to drainage procedures [1, 2, 4]. Pleural fluid amylase is the single most important diagnostic procedure. The level of pleural fluid amylase is generally above 1000 U/L (normal levels < 150 U/L) [10, 12, 16, 19]. There is however, no threshold value for it [12]. Numerous pathologies may have raised amylase levels and include paraneumonie effusion, pulmonary tuberculosis, adenocarcinoma of lung, esophageal perforation, liver cirrhosis, leukaemia/lymphoma and malignancies of the pancreas, rectum, and in females, the gynaecological system [8, 18, 23]. Hence, diagnosis requires high amylase levels in the correct clinical setting. Further, amylase levels above 50,000 U/L are characteristic of PPF [10, 19, 24]. Besides, high lipase and albumin levels are also seen [4].

Once PPF is diagnosed, the fistulous track can be visualised using radiologic investigations. Sensitivity of various imaging modalities to delineate the track is variable with values of 47%, 78% and 80% for Computed Tomography (CT), Endoscopic Retrograde Cholangiopancreatography (ERCP) and Magnetic Resonance Cholangiopancreatography (MRCP), respectively [10, 25]. The ability of CT to delineate the fistula track is debatable [1, 19]. It however, depicts changes of pancreatitis (parenchymal changes, duct dilation, fluid collection) [2, 7, 8]. Moreover, CT is the modality of choice to diagnose pleural effusion [1, 4]. A CT performed immediately after ERCP is reported to have greater sensitivity to depict the fistulous communication [16].

ERCP provides information about the ampulla besides depicting ductal anatomy [2, 10]. Moreover, with the advent of pancreatic duct stents, ERCP attains a therapeutic role as well [12, 16]. Numerous complications inherent to ERCP (invasiveness, infection, bleed, perforation and pancreatitis) [12, 15] however, plague its role as the primary modality to diagnose PPF [12]. It fails if fistula is located beyond the site of obstruction [2, 10]. Also, a successful ERCP requires an experienced endoscopist [8, 19].

The role of MRCP in suspected cases of PPF is two fold: to diagnose the presence and site of fistula [2, 3, 11] and to stratify further management [12]. Unlike ERCP, it is non-invasive [2, 3, 11] and helps in visualisation of pancreatic duct beyond strictures [2, 11]. Further, changes in pancreatic parenchyma can also be known. All these features make MRCP imaging modality of choice in PPF [3, 7, 10, 26].

**MANAGEMENT**

Although there are no systematic studies to establish optimum therapy for PPF, an initial conservative approach is employed [1, 4, 12, 15, 18, 19]. Decision to operate or not is then guided by the persistence of pleural effusion beyond 3 weeks and or signs of superinfection [1, 6, 19]. With the advent of endoscopic procedures (endoscopic procedure alone or in combination with medical therapy), surgical intervention became the second line of management [4, 12]. Endoscopic procedures thus, bridged the gap between medical and surgical therapies (besides bridging the disrupted duct! [8, 23, 27, 28]). However, a significant number of patients initially managed by therapeutic endoscopy eventually required surgery [29, 30]. Hence, the need for a treatment algorithm was strongly felt. Wronsik et al. described the role of MRCP to delineate the pancreatic duct which would guide the type of therapy [12] (Table 1).

Managing patients on initial medical therapy was recommended by Rockey et al. and Lipsett et al. Since pancreatic secretions were the source of pleural effusion, the aim was to suppress both basal and food-stimulated release of pancreatic succus [4, 7, 8, 19, 30]. Hence, therapy included prohibition of oral alimentation, naso-gastric aspiration with total parenteral nutrition (TPN) and administration of somatostatin analogues [19, 30]. Besides, thoracocentesis would drain chest secretions. The therapy soon fell into disrepute since a nil-per-oral approach induced intestinal mucosal atrophy with consequent
It thus follows that conservative management should be tried for 2-3 weeks before switching to other modes of treatment. The answer to second question comes from the observation drawn by Wronski et al. The authors describe management based on the anatomy of pancreatic duct as depicted by MRCP [12]. According to them, patients with relatively normal or mildly dilated duct benefit the most from medical therapy (Table 1) [12]. On the contrary, conservative approach is to be avoided in patients with ductal obstruction and or fistulae distal to obstruction[1, 4, 7, 12]. In these subset of patients, endoscopic or surgical methods form the preferred line of management [12].

Pioneered by Saeed [31], ERCP and stent placement revolutionised non-operative therapy for PPF [1, 8]. ERCP no longer remained merely diagnostic; it combined benefits of therapy as well [12, 16]. The placement of stent serves two roles; a) covering the sites of ductal disruption [8, 12, 23, 27, 28] with mechanical occlusion of communication between pancreatic duct and fistula and b) dilation of the duct strictures [4]. The former decreases fistula output while the latter helps reduce ductal pressure [4, 23]. Shah et al. [32] believe that restoration of anatomic continuity by bridging the disruption is more important than dilation of the stricture. The authors describe regression of PPF in a patient who underwent repeat endoscopy to replace a smaller stent with a longer one to bridge the site of disruption [32]. Since PPF is most commonly associated with chronic pancreatitis (CP) and presence of ductal strictures is a common feature of CP, stents placed proximal to the site of disruption may still help by decompressing the duct [8, 14, 31]. This additionally helps in relieving the pain [23, 28]. Further, in cases of failure of stent placement, papillotomy serves a similar function in relieving the pain [23, 28]. This additionally helps in decompressing the duct [8, 14, 31]. This additionally helps in relieving the pain [23, 28].

Endoscopic procedures however, are not devoid of complications [2, 7, 8]. Moreover, their success depends on technical expertise (eg., difficult cannulation) [8, 19] and presence of anatomic variations. Endoscopic ultrasound (EUS) guided rendezvous ERCP, in these cases, is a viable alternative [33, 34]. The procedure involves endoscope guided transgastric puncture of pancreatic duct followed by passage of guidewire across the ampulla. Subsequently, a stent is cannulated over the guidewire and placed in the pancreatic duct [33, 34].

Nasopancreatic drainage is yet another endoscopic method that combines benefits of low intermittent suction (to facilitate drainage and thus fistula closure) and repeated pancreatograms to confirm the closure of fistula without the need to repeat ERCP [16, 27, 28, 35, 36]. The drain is kept in situ for a week followed by placement of endoprosthesis in pancreatic duct [27, 28]. The drawbacks of nasopancreatic drainage include patient discomfort due to nasal tube and the necessity for continued nursing care [16].

Once a stent is placed (using either of the three endoscopic techniques), a diagnostic ERCP is performed every 6 weeks.
to assess closure of the fistula [4]. This is important since stent cannot be left in the pancreatic duct for indefinite period. The stent in long term induces ductal changes that fail to regress even after its removal [30, 37]. Owing to rarity of PPF, the optimal duration for which the stent should be kept in situ is largely unknown [30, 37]. However, a few series describe the time period for endoscopic therapy as 4-12 weeks [4].

Success rates of ERCP guided stent placement have been variable. Khan [38], Pai [39] and Varadarajulu [40] described a success rate of 100%, 96.4% and 55% respectively in their series. The majority of ductal disruptions in the series of Khan and Pai were located in head or body of the pancreas [12, 39, 40]. Low success rate described by Varadarajulu was either due to failed attempt at stent placement or failure to negotiate the stent across the site of ductal disruption [12, 40]. Failed ductal cannulation was also the cause of low success rate in the series described by O’Toole et al. [41]. It thus follows that duct leakage present in head or body of pancreas with favourable anatomy is amenable to ERCP guided stent placement (table 1). However, failure to localise the ampulla and presence of intraduodenal calculi and or ductal strictures pre-empt stent cannulation and prompt surgical intervention. Also, due to recurrent and chronic nature of the disease, many patients treated successfully by endoscopic procedures require a definitive surgery [29, 30].

Surgical intervention is the definitive line of management for PPF. However, surgical procedures are resorted to only after failure of medical or endoscopic treatment [1, 4, 12]. This delay results in increased morbidity and mortality especially in cases with poor chances of spontaneous resolution [7, 12]. MRCP is a valuable tool which helps diagnose this subset of patients (table 1) [12]. MRCP findings of these patients include complete ductal obstruction or ductal obstruction proximal to fistula site or leakage in tail [12]. Thus, a primary and early surgery in these patients might prove safer as well as cost and time saving. King et al. [7] believe that surgical approach should be first line of management in all patients of PPF. The basis for this conclusion was longer periods of treatment and post-operative recovery and higher rates of complications in patients treated surgically after a failed medical/endoscopic procedure [7]. Moreover, success rate of surgical procedure was three times of medical therapy (surgery, 94%; medical management, 33%) [7].

Pancreatic resection and enteropancreatic anastomosis constitute methods of surgical intervention to achieve drainage of pancreatic secretions [1, 4, 7, 8]. An anastomosis with the gut is required in cases of a disrupted duct or a symptomatic pseudocyst [4, 42]. Decompression of pancreatic duct in cases of ductal obstruction proximal to fistula may involve excision of involved portion of obstructed pancreas (eg, distal pancreatectomy with pancreaticojunostomy) [1, 4, 7, 8, 19]. Partial resection of head may be tried if pancreatic head mass obstructs the duct (Frey’s procedure) [25]. An anastomotic surgery might seem better since it preserves pancreatic tissue unlike resection procedures. Pancreatic parenchymal preservation is particularly important as majority of PPF patients have diminished reserves due to CP. The current evidence is however, conflicting and no procedure is superior over the other [43].

CONCLUSION
PPF is a rare cause of pleural effusion. The condition is diagnosed in the correct clinical scenario with very high pleural fluid amylase. MRCP, besides delineating the pancreatic ductal anatomy, also guides management. An initial medical and endoscopic management is recommended. However, since PPF is associated with chronic, recurrent pancreatitis; frequent relapses are seen. Surgical management is the definitive mode of treatment.

Conflict of Interest
Authors declare to have no conflict of interest.

References


