Bilateral Pleural Fluid Caused by a Pancreaticopleural Fistula Requiring Surgical Treatment

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Abstract

A 53-year-old man developed bilateral pleural effusion with respiratory failure. The amylase level in the pleural effusion was elevated. He had neither abdominal symptoms nor abdominal physical findings. Abdominal computed tomography (CT) also showed no abnormalities. Magnetic resonance cholangiopancreatography (MRCP) was non-diagnostic, but endoscopic retrograde cholangiopancreatography (ERCP) and subsequent CT showed a fistula connecting the pancreatic duct with the right pleural cavity. The pleural effusion was refractory to drug therapy, leading to the need for surgical intervention. The pathological findings revealed chronic pancreatitis without pseudocysts. The elevated pancreatic amylase in the pleural effusion offered an important clue to the correct diagnosis.

Key words: pancreaticopleural fistula, pleural effusion, pancreatitis, amylase

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Introduction

A pancreaticopleural fistula is an abnormal communication between the pancreas and pleural cavity due to leakage of pancreatic secretions from damaged ducts. It is most commonly caused by disruption of the pancreatic duct due to chronic pancreatitis, the main cause of which is usually alcoholism in adults, and biliary-duct obstruction in children. It also may be caused by leakage from a pancreatic pseudocyst. Anterior disruption of a pseudocyst or a pancreatic duct leads to leakage of pancreatic secretions into the free peritoneal cavity, producing pancreatic ascites. If the duct is disrupted posteriorly, the secretions leak through the retroperitoneum into the mediastinum via the aortic or esophageal hiatus. Once in the mediastinum, the leak can go through the pleura, entering the chest, and forming a pancreatic pleural effusion. This finding is predominantly present in alcoholic middle-aged men who usually present with dyspnea and a left-sided effusion (1), seldom with a right-

sided effusion (2, 3).

We herein describe a pancreaticopleural fistula presenting as bilateral bloody pancreatic pleural effusions. The effusions were refractory to drug therapy, and the patient underwent surgical intervention. The pathological findings indicated that his pancreaticopleural fistula was caused by chronic pancreatitis, although computed tomography (CT) images showed a normal pancreatic appearance.

Case Report

A 53-year-old man was hospitalized because of bilateral pleural effusion. He had been well until seven days before admission, when he started to experience a dry cough, dyspnea, and heart palpitations. His symptoms had worsened until he could not lie down. He visited a general practitioner and was referred to our hospital because of bilateral pleural effusion and respiratory failure.

He had no known past clinical history, but had smoked 10 cigarettes per day for 33 years. He had been a carpenter and

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Figure 1. Chest radiography (panel A) and CT (panel B) showed bilateral pleural effusion.

Figure 2. Contrast-enhanced abdomen CT showed no abnormality in the pancreas (circle).

had consumed three cups of Japanese sake (70 g of ethanol) daily. A physical examination found clear lungs on auscultation, but the respiratory sounds were reduced in intensity in the bilateral lung fields. His heart sounds were regular and there was no murmur. Neither jugular vein dilation nor peripheral edema were present. The abdominal findings were normal. His temperature was 37.1°C, blood pressure was 96/68 mmHg, pulse was 124 beats per minute, and oxygen saturation by pulse oximetry (SpO₂) was 90% while breathing ambient air. The laboratory findings indicated slight inflammation, as his white blood cell count was 11,210 per

cubic millimeter and his C-reactive protein was 2.2 mg/dL. His serum amylase level was 700 IU/L. He showed hypoxemia: an arterial blood gas analysis while breathing ambient air found a pH of 7.449, PaCO₂ of 41.2 Torr, PaO₂ of 64.2 Torr, HCO₃⁻ of 28.2 mmol/L, base excess of 4.2 mEq/L, and a SaO₂ of 92.9%.

Electrocardiography found an incomplete right bundle branch block. Chest radiography revealed bilateral pleural effusion (Fig. 1A) and CT scans of his chest showed bilateral pleural effusion with compressed lungs (Fig. 1B). A chest tube thoracostomy was performed, and the pleural

Table. Laboratory Data on Admission

[Blood examination]			[Blood examination]		
	on admission	reference range		on admission	
RBCs($\times 10^4/\mu\text{ L}$)	469	(416-552)	PT(sec)	13.0	
Hemoglobin (g/dL)	13.6	(13.2-17.2)	PT-INR	1.19	
Hematocrit(%)	43.2	(39.2-49.2)	APTT(sec)	25.3	
WBCs($/\mu\text{ L}$)	11210	(34-88)			
Neutro(%)	77.0	(40-70)	pH	7.449	
Eosino(%)	3.0	(1-7)	PaCO ₂ (Torr)	41.2	
Baso(%)	1.0	(0-2)	PaO ₂ (Torr)	64.2	
Mono(%)	7.0	(1-10)	HCO ₃ ⁻ (mmol/L)	28.2	
Lymph(%)	12.0	(18-50)	BE(mmol/L)	4.2	
Platelet($\times 10^4/\mu\text{ L}$)	40.7	(11.8-36.4)	SaO ₂ (%)	92.9	
CRP(mg/dL)	2.2	(<0.5)			
BUN(mg/dL)	8.0	(5-22)			
Creatinine(mg/dL)	0.67	(0.60-1.30)			
Na(mEq/L)	139	(134-146)			
K(mEq/L)	4.1	(3.4-4.9)			
Cl(mEq/L)	101	(98-108)			
AST(IU/L)	37	(8-40)			
ALT(IU/L)	34	(5-35)			
Total bilirubin(mg/dL)	0.61	(0.30-1.10)			
γ -GTP(IU/L)	20	(7-50)			
LDH(IU/L)	252	(106-220)			
ALP(IU/L)	190	(100-340)			
Amylase(IU/L)	700	(35-120)			
CPK(IU/L)	259	(10-180)			
Blood Glucose(mg/dL)	110	(60-110)			
Total protein(g/dL)	6.3	(6.8-8.2)			
Albumin(g/dL)	2.7	(3.7-5.2)			

RBCs, red blood cells; WBCs, white blood cells; PT prothrombin time; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; CRP, C-reactive protein; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; γ -GTP, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; PaCO₂, partial pressure of carbon in alveoli; PaO₂, partial pressure of oxygen in alveoli; BE, base excess; SaO₂, arterial oxygen saturation; PMN, morphonuclear neutrophils; MN, monocytes

fluid was found to be bloody, exudative, mononuclear cell predominant and had markedly increased amylase concentrations (Table). Although abdominal CT scans (Fig. 2) provided no evidence of pancreatitis, a pancreaticopleural fistula was considered to be the indicated diagnosis. Magnetic resonance cholangiopancreatography (MRCP) was non-diagnostic. Endoscopic retrograde cholangiopancreatography (ERCP) clearly showed leakage of the contrast media from the main pancreatic duct of the body and tail of the pancreas to the thoracic cavity (Fig. 3A). Abdominal CT after ERCP also showed a fistula (Fig. 3B). The diagnosis was therefore pancreatic pleural effusion caused by a pancreaticopleural fistula.

We considered placing pancreatic stents or nasopancreatic catheters into the main pancreatic duct endoscopically in order to bridge the site of disruption and to decrease the intra-

ductal pressure. However, it had been technically difficult to perform the ERCP, and we judged that placing pancreatic stents or nasopancreatic catheters would likely be unsuccessful. Moreover, these devices have been reported to cause serious side effects, such as acute pancreatitis, bleeding, perforation, or septic complication. Therefore, we decided not to attempt endoscopic drainage. The patient was first treated by dietary restriction and total parenteral nutrition. Octreotide acetate, a long-acting synthetic octapeptide analogue of somatostatin, was administered subcutaneously to inhibit both basal and stimulated pancreatic exocrine secretion, and to reduce the fistula output, as well as to close the fistula. Despite these treatments, the pleural effusions continued to increase after the chest tube was removed (Fig. 4). Therefore, the patient underwent surgical intervention six weeks after admission. During distal pancreatectomy, inflammatory tight

Figure 3. ERCP showed the fistula and extravasation of contrast material from a pancreatic duct (open arrow) and a cavity (arrow head) in the left chest (arrows) (panel A), the fistula and the extravasation of contrast material from the main pancreatic duct were shown by ERCP (arrows) (panel B).

Figure 4. The results of serial follow-up examinations of the white blood cell (WBC) count, amylase (AMY) level, C-reactive protein (CRP) level, and body temperature (BT). MEPM: meropenem, ABPC/SBT: ampicillin/sublactum

adhesions around the pancreas and spleen were observed. A cord-like structure was present indicative of a ligated fistula, which was therefore extirpated (Fig. 5).

Pathologically, an irregularly-shaped space with fibrin-rich effusion was identified at the center of the pancreas. Degen-

erated fatty tissue was seen around this space. These findings were highly suggestive that it was part of the fistula formation between the pancreatic duct and thoracic cavity (Fig. 6), although the fistula was not apparent pathologically. The main pancreatic duct was shifted toward the upper

Figure 5. Intraoperative findings; a cord indicating the fistula (arrow) was superior to the edge of the pancreas (arrow heads).

side, stenosed near the presumed fistula site, and dilated in the distal part. No pancreatic pseudocysts were present. The histological findings for the background pancreas revealed chronic pancreatitis with fibrosis, mononuclear cell infiltration, dilation, and complicated pancreatic duct branching. The final diagnosis made was chronic pancreatitis, although the patient had neither characteristic abdominal pain nor characteristic CT images showing an inflamed pancreas. Since undergoing surgery, the patient has been well.

Discussion

Although most patients with pancreaticopleural fistulas are alcoholics, only half of them have clinical histories of previous pancreatitis (4). A pancreaticopleural fistula is an unusual complication of chronic pancreatitis, estimated to occur in only 0.4% of patients with chronic pancreatitis and in 4.5% of patients with pancreatic pseudocysts (1). Approximately half (51%) of the patients in that study had a left-sided pleural effusion, 32% had a right-sided effusion, and 16% had bilateral effusion (1). Another study showed that 14% of patients had bilateral pleural effusion (4). A possible mechanism of the pathogenesis of pancreaticopleural fistulas is that the pancreatic enzymes entering into the chest erode the pleural lining and disrupt subpleural vessels, thus causing bleeding into the pleural space. Trauma is a less common cause of pancreaticopleural fistulas, existing in from 0 to 5% of reported cases (5). Pancreatic pseudocysts have been found in 69 to 77% of patients with pancreaticopleural fistulas (5). The underlying mechanism of pancreaticopleural fistula formation usually is leakage from a ruptured pseudocyst or direct pancreatic duct leakage. The clinical presentation is often misleading, as respiratory, rather than abdominal, symptoms predominate.

Our present case was out of the ordinary, because the patient had no medical history of pancreatitis, no abdominal symptoms, nor CT scan findings suggesting pancreatitis. As he presented with massive bloody bilateral pleural effusions, other potential causes, including trauma, spontaneous he-

Figure 6. An irregularly-shaped space with fibrin-rich effusion was identified at the center of the body of the pancreas, and indicated part of the fistula (arrow head) (panel A). The histological findings for the background pancreas showed chronic pancreatitis with fibrosis, monocyte infiltration, dilation (panel B) and complicated pancreatic duct branching (arrow) (panel A).

mopneumothorax, and malignancy, were thus considered first.

The markedly elevated amylase in the pleural fluid was the most important laboratory finding. Some authors arbitrarily have defined a pancreaticopleural fistula as a pleural effusion with an amylase content above 1,000 IU/L and protein above 3.0 g/dL (6). Pleural effusions caused by a pancreaticopleural fistula, however, commonly show amylase levels of several thousand units (4). In fact, in the present case, the amylase concentration in the right pleural effusion was 19,747 IU/L and that in the left was 67,639 IU/L (amylase isoenzyme analysis showed the amylase to be 100% pancreatic amylase). The serum levels of amylase usually are mildly elevated and are thought to be partly secondary to amylase resorption from the pleural surfaces (4). Our patient's serum amylase concentration was 700 IU/L (normal range 35-120). Effusions associated with acute pancreatitis, esophageal perforation, and a thoracic or pancreatic malignancy need to be considered when making a differential diagnosis of elevated amylase pleural fluid, but are usually easy to exclude. In acute pancreatitis, pleural effusion is caused by a reactive inflammatory change that is generally smaller and associated with a lower amylase concentration.

CT is an excellent modality for defining pancreatic abnormalities and should be the first abdominal imaging study used in suspected cases. CT has revealed pseudocysts in 79% of cases with pancreaticopleural fistulas, and there was

extension into the mediastinum in 42% of reported patients (4).

ERCP and MRCP are the modalities commonly used to show a fistulous tract. MRCP is reported to detect pancreatic duct abnormalities and calculi with an accuracy similar to that of ERCP (7). MRCP seems to be the best first-line diagnostic tool for confirmation of a pancreaticopleural fistula, but because it is an invasive procedure, there is a small but substantial complication rate that includes acute pancreatitis, sepsis, and bleeding (8). MRCP is a non-invasive imaging method used to assess pancreatic disease. Because no contrast material is injected, there is no risk of infection or allergic reaction. It has been suggested that diagnostic ERCP should be performed only in confusing cases, because the site of fistulization and anatomic relationships can generally be precisely defined by MRCP (9).

No systematic studies have yet been done to evaluate medical versus surgical therapy. Traditionally, initial 2- to 4-week trials of medical therapies have been performed which prohibit oral intake and utilize total parenteral nutrition, chest tube thoracostomy, and the possible administration of somatostatin or an analog. Somatostatin is a tetradecapeptide that has a wide spectrum of inhibitory gastrointestinal effects. It decreases gut motility and reduces splanchnic blood flow, and dramatically affects pancreatic secretions, inhibiting both basal and stimulated pancreatic exocrine secretions. Octreotide acetate is a long-acting synthetic octapeptide analogue of somatostatin. Its properties are similar to those of somatostatin, but it has the advantage of a much longer serum half-life, and therefore can be administered subcutaneously. Treatment with octreotide appears to significantly reduce fistula output and decrease the time taken to close the fistula (4). The major complication of this treatment for patients is superinfection, which can result in significant morbidity and mortality (4). This conservative medical approach is reported to have achieved a resolution of pancreaticopleural fistula in 31% to 65% of adult cases (4, 8, 10). Failure of such conservative medical treatment is considered to be an indication for endoscopic or surgical intervention, and there are many reports of patients successfully treated by endoscopic procedures (6, 8, 11-13).

Endoscopy, however, may produce serious side effects, such as acute pancreatitis, bleeding, perforation, or septic complications. Complication rates of from 7% to 25% have been reported (14-16). Nevertheless, it has been suggested that pancreaticopleural fistulas may be best managed by ERCP-guided therapeutic intervention or by early surgical treatment (17). Medical therapy was reportedly successful in only 31% of patients, whereas surgical therapy was more than three times as likely to succeed (94%) in one study (17). In addition, it took more than twice as long to treat patients medically than was needed for postoperative recovery, thus providing further evidence that early surgical intervention may decrease the duration of treatment required for fistula resolution.

In their review article entitled "Pancreaticopleural fistula"

Ali, et al. described that they had identified case reports and case series of pancreatic pleural fistulas in the English literature from 1960 to 2007 in the PubMed, OVID, and EMBASE search engines (8). A total of 222 patients with pancreatitis and pleural effusion had been reported in the English literature, however, 159 patients had not had a confirmed diagnosis of a pancreatic pleural fistula. Therefore, they could identify only 52 cases of pancreatic pleural fistula. Twenty-one patients (65%) improved with conservative management alone. Interventional therapy (five endoscopic and six surgical interventions) were eventually needed in 35% of the patients after the failure of conservative management.

In conclusion, we treated a patient with pancreatic pleural effusion caused by a pancreaticopleural fistula. He had no abdominal signs or symptoms and showed normal findings on abdominal CT scans. Markedly elevated amylase levels in his pleural fluid provided an important diagnostic clue. MRCP was non-diagnostic, whereas ERCP followed by CT clearly showed the fistula. The pancreatic pleural effusion was refractory to medical therapy, but the patient successfully underwent distal pancreatectomy, and has since been doing well. Pathologically, the final diagnosis was chronic pancreatitis.

The authors state that they have no Conflict of Interest (COI).

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