CASE REPORT

Pancreatic Juice Culture in Acute Pancreatitis and Other Pancreatic Disorders

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ABSTRACT

Objectives We retrospectively evaluated the results of pancreatic juice cultures of patients with acute pancreatitis and other pancreatic disorders. **Methods** Twenty patients who underwent pancreatic juice culture were studied. Nine had acute pancreatitis due to alcohol (n=5), idiopathic causes (n=2), drugs (n=1), or gallstones (n=1), and remaining 11 had other pancreatic disorders such as an intraductal papillary mucin-producing neoplasm (n=3) and main pancreatic duct dilatation with a stricture due to a tumorous lesion suspected of pancreatic cancer (n=7) or chronic pancreatitis (n=1) without symptoms. Nasopancreatic drainage tubes were placed for pancreatic duct drainage in acute pancreatitis and for pancreatic juice cytology in other disorders. Pancreatic juice was obtained through the drainage tube and cultured. **Results** Pancreatic juice cultures were positive in all patients with acute pancreatitis for *Staphylococcus epidermidis*, *Streptococcus* species, and others. Six among 11 patients (54.5%) with other disorders showed positive results for *Escherichia coli, Streptococcus salivarius,* and others. The rate of positive pancreatic juice cultures was significantly higher in acute pancreatitis (p=0.038). Seven of the 9 patients with acute pancreatitis were classified as having severe acute pancreatitis, and all survived treatment. **Conclusions** Pancreatic juice culture was highly positive in acute pancreatitis. Further study is needed to confirm the relationship between orally indigenous bacteria identified in the pancreatic juice and acute pancreatitis.

INTRODUCTION

Various mechanisms such as an obstruction, toxicity, drugs, post-surgical complications, genetics, bacterial infection, viral infection, trauma and cancer [1, 2, 3] are assumed to be responsible for acute pancreatitis (AP) and are well characterized. However, mortality of acute pancreatitis remains high [4], and an effective treatment strategy to reduce the mortality has not been established.

Trypsinogen activation has generally been considered as the key event in the initiation of AP and is known as the "trypsin paradigm" [5]. Recently, it has become clear that the activation of inflammatory signaling mechanisms in acinar cells is crucial to the pathogenesis of pancreatitis [6]. A candidate mediator of the inflammatory response in AP is the transcription factor, NF-κB [7]. The activation of NF-κB occurs within pancreatic acinar cells early in the course of AP and is able to provoke pancreatic and systemic inflammatory responses, correlating with the expression of cytokines and chemokines [8]. Activation of NF-κB is caused by various factors, including bacterial infection [6, 9].

The possibility of infection as a cause of AP was advocated in the late 19th century, although it was discounted in the early 20th century [10]. However, in chronic pancreatitis, it has been reported that bacteria are commonly identified in the pancreatic juice, with positive findings in 42% of the cases [11]. Moreover, the hemodynamic consequence of severe AP was described to be the same phenomenon, with sepsis and infection assumed to be the key mechanisms for the development of severe AP [12]. Another report described that the pancreatic juice cultures were positive for bacteria in 31.4% of pancreatitis and pancreatic cancer cases [13]. In this report, 35 patients were examined, out of which 25 and 10 patients had acute relapsing pancreatitis and chronic pancreatitis, respectively. Six and 5 patients with each disorder underwent pancreatic juice culture during an acute episode and had 100% positive results. Ten of these 11 patients had abnormalities of the pancreatic ducts. Identified bacteria included *Escherichia coli*, *Enterococcus, Enterobacter, Klebsiella, Pseudomonas, Proteus, Acinetobacter calcoacetius, Group D streptococcus, Staphylococcus aureus, Minia,* and *Candida.* The former 3 species were the major bacteria. However, the author did not describe which bacterium was identified in each disorder.

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During the early clinical course of AP, abnormalities in laboratory data of varying degree, including increased white blood cell (WBC) counts and elevated inflammatory reactions, are seen. In patients showing these abnormalities, along with a complaint of fever and upper abdominal pain, the condition was diagnosed as an infectious disease. Therefore, a possible mechanism for AP could be the infection [14], and bacterial infection could be responsible for the activation of NF-κB during AP in some cases.

In patients with AP and persistent, severe pain, in spite of repeated administration of an analgesic, along with remarkably increased WBC counts, we placed a nasopancreatic drainage (NPD) tube for pancreatic duct drainage because of a suspicion of pancreatic juice infection. The results of pancreatic juice culture from patients with AP and other pancreatic disorders without symptoms were retrospectively evaluated in this study.

METHODS

Twenty patients who underwent culture of pancreatic juice between 2010 and 2015 were included in this study (12 men, 8 women; median age 64.5 years, range 35-86 years) **(Table 1)**. Among these patients, 9 (7 men, 2 women; median age 49 years, range 35-73 years) had AP due to alcohol (n=5), idiopathic causes (n=2), drugs, (n=1), or gallstones (n=1). The patient with drug-induced pancreatitis took corticosteroids for asthma. Alcoholic-induced AP was defined on the basis of the evidence of sustained and uncontrolled consumption of alcoholic beverages and/or excessive alcohol consumption (defined as a drunken state in the patient's history) in the week prior to admission while excluding other causes of AP [15]. Idiopathic pancreatitis was diagnosed when the clinical, laboratory, and conventional radiologic methods did not provide a clear etiology for the episode [16]. When persistent, severe abdominal pain, despite administration of analgesics occurred more than 3 times over a 12-h period , along with an increased WBC count or fever, endoscopic placement of a 5-Fr pigtail NPD tube (Olympus, Tokyo, Japan) **(Figure 1)** was performed. This was done in 7 of the 9 patients due to the possibility of a pancreatic juice infection. In 1 patient with idiopathic pancreatitis, massive ascites with high levels of amylase content (5,400 U/L), diagnosed as pancreatic ascites was found, and NPD tube placement was performed for the treatment of this disorder [17]. The remaining patient, with gallstone pancreatitis, underwent pancreatic duct drainage with NPD placement during endoscopic retrograde cholangiopancreatography (ERCP). This was done to avoid exacerbation of the AP due to biliary stent placement, which was necessary because the major papilla was swollen, narrowing the orifice. All patients underwent antibiotics administration after admission before ENPD placement. In 6 patients, pancreatic juice was obtained once for culturing within a few minutes after NPD tube placement. In the remaining 3 patients, the volume of pancreatic juice flowing out from the NPD tube was too little to culture just after NPD tube placement and pancreatic juice for culturing was obtained once a couple of days after the placement because pancreatic juice volume recovered gradually after the placement.

The remaining 11 patients (5 men, 6 women; median age 71 years, range 38-86 years) had dilation of the main pancreatic duct (MPD) due to an IPMN (n=3) or a stricture of the main pancreatic duct due to a tumorous lesion suspected of pancreatic cancer (n=7) or chronic pancreatitis (n=1) without symptoms **(Table 1)**. NPD tubes were placed to collect pancreatic juice for repeated cytology because of the suspicion of malignancy [18]. Part of pancreatic juice obtained within a few minutes after NPD tube placement was used for culturing once.

For NPD tube placement, pancreatography was performed through the major papilla to estimate problems in the main pancreatic duct, including stenosis and a filling defect, especially in AP by using a small amount of contrast medium. A 0.025-inch guidewire (Jagwire, Boston Scientific, Natick, MA, USA) was introduced into the upper stream of the main pancreatic duct, and an NPD tube was placed. If the guidewire could not be introduced to the upper stream due to a malformation of the pancreatic duct, such as an incomplete pancreas divisum, the minor papilla was selected for introducing the guidewire and placing the NPD tube. Subsequently, the pancreatic juice was obtained through the tube.

We retrospectively evaluated the results of pancreatic juice culture from patients with AP and other pancreatic disorders. In AP, APACHE II and Ranson scores were estimated to evaluate the severity. The clinical course and the state of the pancreatic duct on pancreatography were also analyzed.

Table 1. Patient characteristics.

		n=20
Male/Female		12/8
Median age (y)		61 (35-86)
Acute pancreatitis		9
	Male/Female	7/2
	Median age (y)	49 (35-73)
	Etiology alcohol	5
	idiopathic drug	2
	gallstone	1
		1
Other disorders		11
	Male/Female	5/6
	Median age (y)	71 (38-86)
	Etiology	
	IPMN	3
	Suspected pancreatic cancer	7
	Chronic pancreatitis	1

IPMN intraductal papillary mucin-producing neoplasm

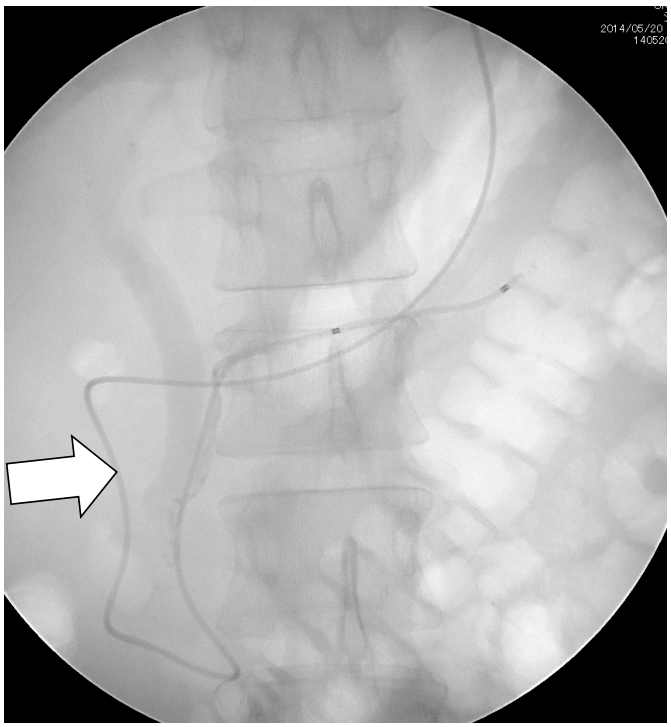

Figure 1. Endoscopic placement of a 5-Fr pigtail nasopancreatic drainage tube. Nasopancreatic drainage (NPD) tube (arrow) was placed via the duodenal major papilla. Cholangiogram is also revealed.

Statistical analysis was performed using the t-test. Difference was considered to be statistically significant at a *p*-value of less than 0.05.

RESULTS

In all patients with AP, the pancreatic juice culture was positive for bacteria **(Figure 2)**, showing *Staphylococcus epidermidis* (n=3), *Streptococcus* species (n=2), *Streptococcus* species with *Enterobacter cloacae* (n=1), *Streptococcus* species with *Enterococcus* species (n=1), *Streptococcus agalactiae* in (n=1), and *Enterococcus faecalis* (n=1) **(Table 2)**. *E. faecalis* was identified from the pancreatic juice of the patient with gallstone pancreatitis, whose bile was also positive for *E. faecalis.* On the other hand, in patients with other disorders, pancreatic juice cultures were positive for bacteria in 6 of the 11 patients (54.5%) **(Figure 2)**. The bacteria identified in these patients were *Escherichia coli* (n=1), *Streptococcus salivarius* (n=1), *Streptococcus mitis* with *Streptococcus* species, and *Bacteroides* species (n=1), *Streptococcus intermedius* with *Bifidobacterium* species (n=1), *and Klebsiella pneumonia* (n=1), **(Table 2)**. The incidence of positive results from the cultures was significantly higher in patients with AP (*p*=0.038).

In patient with AP, APACHE II scores were greater than 8 points in 7 patients (range 22-4, median 8) with the highest score of 22 points in the patient with multiple organ failure due to gallstone pancreatitis **(Table 3)**. The Ranson scores were greater than 3 points in 2 of the patients (range 4-1, median 1). The highest score (4) was in the patient with gallstone pancreatitis. WBC counts and CRP levels were 8,100-28,800/μL (median 16,500/μL) and 0.04-23.4 mg/dL (median 1.35 mg/dL), respectively.

In the 7 patients with AP who underwent NPD tube placement, AP was classified as severe based on APACHE II scores over 8 or Ranson scores over 3. In spite of APACHE II scores below 8 or Ranson scores below 3, 2 patients underwent NPD tube placement because of high fever, with a body temperature over 38.0°C, and increased WBC counts (17800/μL and 28,800/μL), suggesting pancreatic juice infection. All of the 9 patients were discharged alive. NPD tubes were placed on the 1st (n=2), 2nd (n=5), 3rd (n=1), and 5th (n=1) day **(Table 3)**. Six patients had abnormal findings, including pancreatic duct stenosis with disruption of the upper stream (n=2), calculi (n=2), incomplete pancreas divisum (n=1), and stenosis with calculi (n=1). In 2 patients with idiopathic pancreatitis, a yellowish pancreatic juice was collected. Both samples included bile. One also had a protein plug and a total bilirubin concentration of 5.7 mg/dL. The other had a total bilirubin concentration of 57.3 mg/dL. Abdominal pain was relieved after the procedure and repeated administration of analgesics became unnecessary within 1-8 days (median 4 days). NPD was kept in place until a meal could be taken

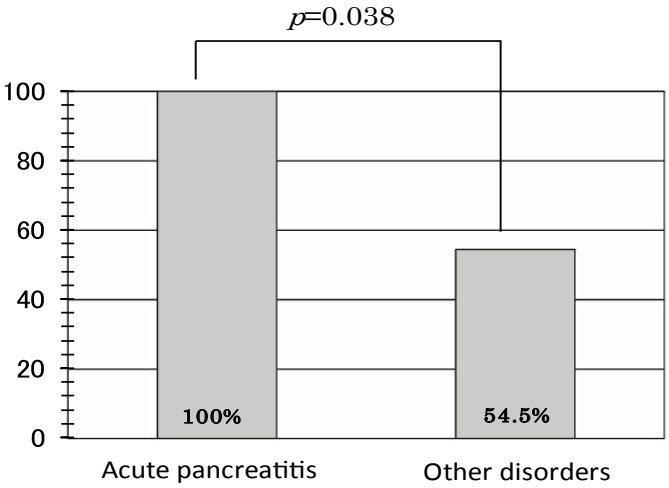

Figure 2. Ratio of positive pancreatic juice cultures. All patients in acute pancreatitis had positive pancreatic juice cultures. The ratio (100%) was significantly higher than that of other disorders (54.5%) (*p*=0.038).

Table 2. Identified bacteria in pancreatic juice.

Disorder	Identified bacteria	n
Acute pancreatitis		
	Staphylococcus epidermidis	3
	Streptococcus species	2
	Streptococcus species plus *Enterobacter cloacae*	1
	Streptococcus species plus *Enterococcus*	1
	Streptococcus agalactiae	1
	Enterococcus faecalis	1
Other disorders		
	Streptococcus salivarius	1
	Streptococcus mitis plus *Streptococcus species* plus *Bateroides* species	1
	Streptococcus intermedius plus *Bilidobacterium* species	1
	Klebsiella pneumonia	1
	Enterococcus faecalis	1
	Escherichia coli	1

without complications. The period of NPD placement was 2-34 days (median 14 days). All patients were discharged and the duration of hospitalization was 10-43 days, with a median of 21 days.

In other disorders, WBC counts and CRP levels were 3500-9100/μL (median 5600/μL) and 0.002-6.6 mg/dL (median 0.46 mg/dL), respectively **(Table 4)**. Four of the 11 patients had pancreatic juice cytology results that were positive for pancreatic cancer.

DISCUSSION

Several mechanisms such as an obstruction, toxicity, drugs, post-surgery complications, genetics, bacterial infection, viral infection, trauma, and cancer [1, 2, 3] are assumed to be responsible for acute pancreatitis (AP) and are well characterized. However, mortality of acute pancreatitis remains high [4], and an effective treatment strategy to reduce the mortality has not been established. In AP, some patients have a fever with inflammatory reactions found on blood examination, suggesting that the disorder could be an infectious disease.

Herein, we performed pancreatic duct drainage only in patients with severe pain and fever who had clinical features consistent with an infectious disease. In our study, bacteria were also identified among half of patients in other disorders than acute pancreatitis, having MPD dilatation without symptoms. This shows that bacteria are not rare in the pancreatic juice, which agrees with a previous report [11]. On the other hand, the occurrence ratio of positive pancreatic juice cultures was significantly high in AP patients (100%). This result is similar with that of the previous report describing the pancreatic juice culture in pancreatitis [13], and suggests that bacterial infection in the pancreatic juice could be associated with AP. However, the bacterial profiles with indigenous bacteria included in all patients of AP were slightly different from the profiles of those with other disorders and with bacterial profile of patients with pancreatitis in previous reports [13]. The cause for this difference is still unresolved. We suspect that *S. epidermidis* and *S. agalactiae* are primarily responsible for onset of AP because these bacteria behave as virulent pathogens [19, 20] with adhesion to human membranes or production of toxins. Bacteria mentioned in the previous report on pancreatitis, such as *E. coli* or *Klebsiella* species [13], secondarily infect the injured tissue of the pancreas during the course of AP after being translocated from the intestine [21]. Usually, *Streptococcus* species and *Staphylococcus* species, including the indigenous bacteria of the mouth or the skin, do not cause diseases and maintain a benign relationship with the host [20]. However, they can sometimes cause severe infections, including liver and brain abscess, and endocarditis when acting as virulent pathogens [22, 23, 24].

Our results of pancreatic juice culture in AP could be due to contamination of the indigenous bacteria of the mouth or the skin by using the endoscope that was introduced into the duodenum, cannulation to the papilla, or extraction of the drainage tube through the nose. However, the lower occurrence of positive pancreatic juice cultures and the bacterial profile with the lower rate of detection of indigenous bacteria in other disorders suggest that the results of AP were not just due to bacterial contamination of the sample during endoscopic procedures. If bacterial contamination were strongly associated with the results of bacterial culture in AP, the same results could be expected in other disorders. Moreover, 6 of the 9 AP patients, had some findings in the main pancreatic duct, including disruption of the main pancreatic duct with the down-stream stricture and pancreatic calculi. This result is also similar with the previous report describing the pancreatic juice culture in pancreatitis [13]. These abnormalities might become the requirement and be responsible for the infection by causing a disturbance in the flow of pancreatic juice.

The route of infection is assumed to be due to a reflux from the duodenum into the pancreatic duct or the hematogenous nature. Hypotonia of the sphincter of Oddi might allow a reflux from the duodenum [25]. It was reported that alcohol can significantly reduce the baseline contractile amplitude of the sphincter of Oddi [26]. Duodenal bacterial flora contains *Streptococcus* species [27], and reflux from the duodenum could be

Table 3. Characteristics of acute pancreatitis.

		n=9
APACHE II score (points)	4 - 22	median 8
Ranson score (points)	1-4	median 1
WBC (/μL)	8,100 - 28,800	median 16,500
CRP (mg/dL)	0.04 - 23.4	median 1.35
Severe acute pancreatitis (n)	7	
The hospital day of NPD placement (day : n)	1^{st} /2^{nd} /3^{rd} /5^{th}	: 2/5/1/1
Pancreatic duct abnormalities (n)	6	
Stenosis with disruption / Calculi / Incomplete pancreas divisum / Stenosis with calculi	2 / 2 / 1 / 1	
Pancreatic juice abnormality (n) (contained bile)	2	
Abdominal pain relief (days after NPD placement)	1 - 8	median 4
Period of NPD placement (days)	2-34	median 14
Hospitalization (days)	10-43	median 21

CRP C-reactive protein; NPD nasopancreatic drainage; WBC white blood cell

Table 4. Characteristics of other disorders.

		n=11
WBC (/μL)	3,500 – 9,100	median 5600
CRP (mg/dl)	0.002 - 6.6	median 0.46
Positive cytology (n)	4	

CRP C-reative protein; WBC white blood cell

responsible for the onset of AP. Additionally, alcohol can induce bacterial overgrowth in the intestine [28] and bacterial translocation from the intestine [29]. In our study, 5 of the 9 patients with AP had alcoholic pancreatitis. Some identified bacteria in this study belong to indigenous bacteria of the mouth and others belong to the intestinal flora. Alcohol may induce translocation of those bacteria via the oral or the intestinal mucosa. Moreover, a fragile condition of the main pancreatic duct is induced by alcohol [30]. This phenomenon has been reported to be caused by apoptosis due to the generation of reactive oxygen species, depolarization of the mitochondrial membrane potential, and activation of the caspase-3 enzyme, and may also be responsible for bacterial infection of the pancreas and the onset of AP. One patient in our study took steroids for asthma, and steroids reduce mucosal IgA production, resulting in a decline of the ability to defend against bacterial infection [30, 31]. This may result in excessive bacterial translocation via the oral or pharyngeal mucosa and be responsible for onset of AP.

Two patients had bile in their pancreatic juice, which was aspirated through the NPD tube with a total bilirubin concentration of 5.7 mg/dL and 57.3 mg/dL. Abnormal duodenal papilla function might be responsible for the reflux of bile into the pancreatic duct and may have induced AP in patients diagnosed with idiopathic pancreatitis. The 2 patients did not have any hepatobiliary abnormalities on blood examination or diagnostic imaging, thus, gallstone passage through the duodenal papilla or gallstone impaction of the common channel was unlikely to be the cause of AP in these cases. Bile, especially when infected, has been reported to induce AP [32]. In the 2 patients diagnosed with idiopathic pancreatitis, their pancreatic juice cultures were positive for *Staphylococcus* species. The phenomenon of bile reflux into the pancreatic duct might be the key mechanism for the onset of idiopathic AP.

All patients underwent pancreatic duct drainage to treat AP, including 6 cases of severe AP, and survived this treatment. However, proper candidate selection is crucial for this treatment. In our study, alcoholic pancreatitis with abnormal laboratory results suggesting infectious disease and the presence of severe pain in spite of repeated administration of analgesics were present in the majority of AP patients. This information may contribute to the process of selecting candidates for pancreatic drainage. Endoscopic treatments for AP have been reported, however, the subjects for treatment were limited to patients with gallstone pancreatitis, congenital anomalies including pancreas divisum, sphincter Oddi dysfunction, and idiopathic pancreatitis [33, 34]. Our study could suggest the criteria for a new group of patients with AP as candidates for ERCP.

For pancreatic duct drainage, placement of either a pancreatic stent or an NPD tube could be selected. A pancreatic stent enables pancreatic juice to flow into the duodenum and reduce the intraductal pressure on the pancreatic duct, which could lead to the repair of damage to the pancreatic duct [35]. However, stents also allow duodenal fluid reflux into the pancreatic duct, which may raise the intraductal pressure on the pancreatic duct and hinder repair of the pancreatic duct. Stents are also easily occluded [36, 37, 38]. On the other hand, NPD has the advantage of constantly decreasing intraductal pressure on the pancreatic duct to levels lower than the duodenal cavity, maintaining the integrity of the pancreatic duct environment, preventing infection, and avoiding reflux of duodenal juice into the injured pancreatic duct [37, 39], which may contribute to the repair of pancreatic duct damage and prevent worsening of pancreas inflammation. The use of NPD tubes also allows for the evaluation of the pancreatic duct when needed [37, 40]. However, a drawback of NPD is that patients must endure transnasal placement of a drainage tube.

In conclusion, pancreatic juice culture was highly positive in acute pancreatitis, and further study is needed to confirm the relationship between orally indigenous bacteria identified in the pancreatic juice and acute pancreatitis.

Conflicting Interest

The authors declare no conflict of interests for this article.

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