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ORIGINAL ARTICLE

Rapid Evolution from the First Episode of Acute Pancreatitis to Chronic Pancreatitis in Human Subjects

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ABSTRACT

Context Growing evidence suggests that recurrent acute pancreatitis leads to chronic pancreatitis, but this sequence is seldom reported in human subjects. The sentinel acute pancreatitis event hypothesis suggests that an initial episode of acute pancreatitis is the first step in a complicated series of events ultimately leading to chronic pancreatitis.

Objective To identify patients who evolved from recurrent acute pancreatitis to chronic pancreatitis.

Setting The Severity of Acute Pancreatitis Study (SAPS) database was reviewed.

Patients Four out of 102 enrolled patients fulfilled the above sequence of events: progression from a single self-limited episode of acute pancreatitis to recurrent attacks to chronic pancreatitis proven by CT scan. However, not all 102 enrolled patients were followed with CT scans; hence there may be more patients with progression.

Results In all four patients, upon initial presentation, there was no evidence of chronic pancreatitis on the CT scan performed and no clear acute pancreatitis etiology was identified. They were asymptomatic between recurrent attacks. All patients progressed to chronic pancreatitis over a relatively short period of time. Two patients were positive for *SPINK1* mutations (N34S), and underwent pancreatectomy with pancreatic islet autotransplantation.

Conclusion The presented patients seem to fulfill the sentinel acute pancreatitis event hypothesis. Their clinical course supports the concept that pancreatitis may be an entity with a broad spectrum of end-points ranging from an isolated episode of acute pancreatitis evolving to chronic pancreatitis.

INTRODUCTION

Acute, recurrent acute and chronic pancreatitis are pancreatic inflammatory syndromes defined by clinical and pathological criteria [1, 2]. Acute pancreatitis is an event initiated by pancreatic injury leading to an acute inflammatory response and associated complications [3]. The syndrome of recurrent attacks of acute pancreatitis in a pancreas with otherwise normal morphology is referred to as recurrent acute pancreatitis [4]. Chronic pancreatitis is defined as chronic pancreatic inflammation with progressive fibrosis, sclerosis and parenchymal atrophy which is often associated with permanent loss of exocrine and endocrine function with variable pain levels [1, 2, 5, 6, 7].

The question as to whether acute and chronic pancreatitis are independent processes or

whether acute pancreatitis is a prerequisite for chronic pancreatitis has been controversial. Growing laboratory, pathologic and epidemiologic evidence suggests that recurrent acute pancreatitis leads to chronic pancreatitis, but this sequence is seldom reported in individual patients [8]. The aim of our study was to identify patients who progressed from recurrent acute pancreatitis to chronic pancreatitis over time, highlight their varying management options and attempt to shed more light on the possible link between acute, recurrent acute and the chronic forms of this disease.

METHODS

We performed a retrospective observational analysis of patients prospectively evaluated following their initial episode of acute pancreatitis, in the Severity of Acute Pancreatitis Study (SAPS) database [9]. Four out of 102 enrolled patients fulfilled the above sequence of events: progression from a single self-limited episode of acute pancreatitis to recurrent attacks to chronic pancreatitis proven by CT scan. All 102 enrolled patients were not necessarily followed by computerized tomography (CT) scanning; hence there may be some inherent negative bias as more than four patients may have pathologically progressed. Patients were tested for *PRSS1* gene mutations (R122H, N29I, A16V and K23R), *CFTR* gene sequencing and *SPINK1* N34S polymorphism.

RESULTS

Table 1 summarizes the characteristics of the four SAPS patients.

Patient A

She experienced her first episode of acute pancreatitis at 13 years, presenting with classical symptoms of abdominal pain and elevated pancreatic enzymes. Family history was positive for pancreatic pathology (Table 1). Initial work up revealed a normal abdominal ultrasound with a CT scan consistent with acute pancreatitis. She was managed conservatively. Over the following two years, the patient had similar recurrent episodes occurring at 3 to 4 monthly intervals. Her work-up failed to identify a clear etiology. Following her fourth acute pancreatitis attack, an elective cholecystectomy was performed. After her fifth attack, she displayed signs of chronic

Table 1. Patient characteristics.

	Patient A	Patient B	Patient C	Patient D
Age at first attack (years)	13	16	13	58
Gender	Female	Male	Male	Female
Presumed Etiology	Idiopathic	Idiopathic	Idiopathic	Idiopathic
Family history of pancreatitis	Brother with recurrent acute pancreatitis	None	None	None
No. of acute pancreatitis attacks/year	4	6	5	8
Time interval between initial attack and development of chronic pancreatitis (years)	1.5	3	3.5	2
Genetic testing	*PRSS1* -/- *SPINK1* +/+ *CFTR* -/-	*PRSS1* -/- *SPINK1* +/- *CFTR* -/-	*PRSS1* -/- *SPINK1* -/- *CFTR* -/-	*PRSS1* -/- *SPINK1* -/- *CFTR* -/-
Follow up	Total pancreatectomy and pancreatic islet cell autotransplantation	Total pancreatectomy and pancreatic islet cell autotransplantation	Enzyme replacement and pain medications	Enzyme replacement and pain medications

pancreatitis to include progressive calcification on CT scans (Figure 1). Serial endoscopic retrograde cholangiopancreatograms (ERCPs) with pancreatic sphincterotomy and pancreatic duct stent placement were performed over time. Progressively, her pain became constant requiring chronic narcotic utilization. Four years following presentation, a complete pancreatectomy, splenectomy, roux-en-Y gastrojejunostomy and pancreatic islet auto transplantation was performed because of the frequency and severity of the patient's symptoms. The patient is now 6 years since initial presentation and is clinically well since this intervention, requiring 6 units of insulin gargline per day.

Patient B

He presented with his first episode of acute pancreatitis at 16 years of age. Conservative management successfully relieved his symptoms. His CT scan was consistent with acute pancreatitis without evidence of chronic pancreatitis. No discernable etiology was identified. The patient suffered from recurrent episodes of acute pancreatitis once every two months. All attacks were conservatively managed. At 18 years, he underwent a laparoscopic cholecystectomy. His gallbladder revealed evidence of small gallstones with a normal intraoperative cholangiogram. He continued to experience recurrent attacks and underwent several ERCPs with biliary and pancreatic sphincterotomies. One year later, progressive pancreatic calcifications were identified on abdominal CT scan. ERCP confirmed ductal changes consistent with chronic calcific pancreatitis. Five years following presentation, a complete pancreatectomy with pancreatic islet autotransplantation was performed. Post operatively he experienced intermittent episodes of nausea and abdominal pain suggestive of small bowel obstruction. An exploratory laparotomy corrected internal herniae through the transverse mesocolon. The patient is currently doing well and is placed on a NovoLog® (Novo Nordisk A/S, Copenhagen, Denmark) insulin pump.

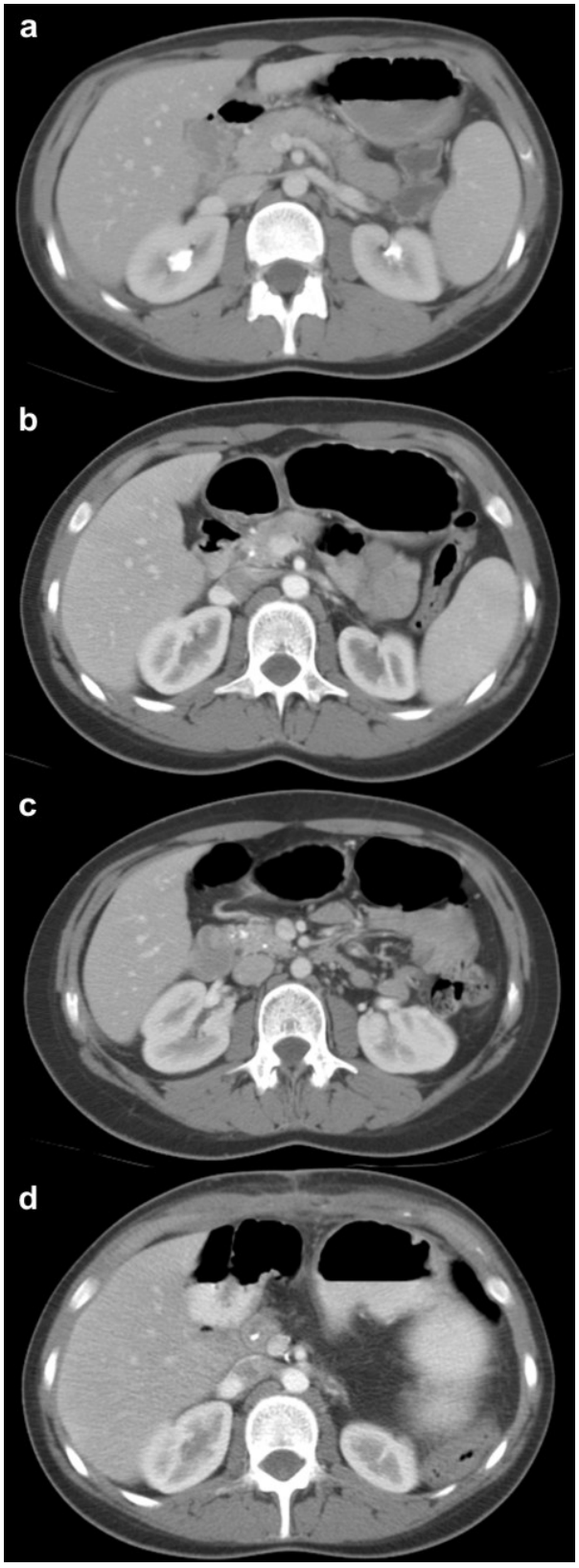

Figure 1. Progressive serial CT scans over 6 years (Patient A). **a.** Initial presentation CT does not show any evidence of chronic pancreatitis. **b. c.** Progressive calcification identified suggestive of chronic pancreatitis. **d.** Following pancreatectomy and pancreatic islet cell autotransplantation.

Patient C

He had his first episode of acute pancreatitis at 13 years, which was attributed to blunt abdominal trauma following a bicycle accident. An ERCP was normal. One year following presentation, an elective cholecystectomy was performed after an ultrasound showed biliary sludge. One year later, he experienced recurrent attacks of acute pancreatitis often requiring prolonged hospitalization with total parenteral nutrition. Etiology workup was negative. He progressively demonstrated evidence of chronic pancreatitis by CT and ERCP. Nine years following his first episode, the patient is currently managed by pancreatic enzyme replacement and pain medications.

Patient D

She had her first episode of acute pancreatitis at age 58. At the time, she underwent a cholecystectomy after a right upper quadrant ultrasound revealed gallstones. Within a month, she experienced a recurrent attack of acute pancreatitis. A CT scan of the abdomen revealed an area of decreased attenuation in the uncinate process without any signs of chronic pancreatitis. A follow-up endoscopic ultrasound showed hyperechoic strands and foci in the uncinate process, but no evidence of dilated side branch or a cystic lesion. The patient suffered recurrent episodes of acute pancreatitis every 6 weeks and was treated conservatively. A repeat CT scan performed after her fourth attack showed resolution of the previously described abnormal uncinate process lesion and a small pseudocyst in the pancreatic body. She underwent ERCP with pancreatic sphincterotomy and pancreatic duct stent placement. Repeat CT scan with her next attack of acute pancreatitis six months later, revealed small calcifications consistent with chronic pancreatitis. Two years following her first episode, the patient is currently managed by pancreatic enzyme replacement and pain medications.

DISCUSSION

The existence of a possible link between acute, recurrent acute and chronic pancreatitis is a controversial issue. The initial definitions of the acute and chronic forms of the disease originated from the Marseilles conferences in the 1960s-1980s [1, 2, 10]. At that time, acute pancreatitis was considered to be a self-limited, completely reversible process. Initially, chronic pancreatitis was defined as a continuous inflammatory process characterized by irreversible morphologic changes that typically led to pancreatic loss of function. Subsequently, chronic pancreatitis was further subdivided into either calcifying or inflammatory subtypes [2]. The entities of acute and chronic pancreatitis were determined to be separate pathological processes. If the two conditions co-existed, then the acute component was considered to be a manifestation of underlying, but previously unrecognized chronic pancreatitis. Recent evidence, however, suggests an alternative hypothesis [8].

The belief that acute pancreatitis is a completely reversible process seems to be changing. Indeed, emerging data suggests that scarring from acute pancreatitis may lead to strictures or pseudocysts that may partially block the pancreatic duct thus predisposing patients to recurrent acute pancreatitis [8]. In addition, a large pathologic case series [11] and studies of hereditary pancreatitis suggest that there is a close relationship between acute, recurrent acute and chronic pancreatitis [12, 13].

Recently, many advances have been identified in the field of pancreatic disease genetics. The first pancreatitis susceptibility gene to be discovered was *PRSS1* (cationic trypsinogen) in families with hereditary pancreatitis [13]. Substitution of arginine with histidine at position 122 eliminates the key autolysis site of trypsin. Prolonged survival of trypsin within the acinar cells leads to acute pancreatitis and recurrent attacks progress to chronic pancreatitis. *SPINK1*, the serine protease inhibitor Kazal-type 1, is a small molecule directly inactivating trypsin within the acinar cells. Substitution of asparagine with serine at position 34 results in increased risk of chronic pancreatitis [14, 15]. Of interest, two of the above reported patients

(Patients A and B) were found to have the latter mutation.

A key molecule in the pancreatic duct is the cystic fibrosis transmembrane conductance regulator (*CFTR*), which is a regulated anion channel located at the luminal surface of the duct cells. New models of pancreatic duct physiology indicate that most of the bicarbonate secretion is mediated through the *CFTR* molecule [8]. It has been recently demonstrated that *CFTR* mutations are very common in idiopathic and alcoholic chronic pancreatitis and some of the 1,250 known *CFTR* gene sequence variants may be pancreas specific [16, 17].

The sentinel acute pancreatitis event model was recently developed in an attempt to classify the multiple risk factors associated with chronic pancreatitis and the different roles of key players, such as the immune system and the pancreatic stellate cells [18]. This model organizes these factors into a hypothetical pathway that commences with an episode of acute pancreatitis and ends in the chronic form of the disease. The initial acute episode results in the activation of the immune system, including stellate cells and recruitment of key cells such as macrophages into the pancreas. Indeed, even if, with time, the pancreas may regain its normal appearing histology after an episode of acute pancreatitis, the inflammatory cells recruited during the episode remain in place and can therefore respond to further stimulating factors. Subjects with inadequate injury protection (e.g. presence of *PRSS1*, *SPINK1* or *CFTR* mutations) who are challenged by metabolic or environmental stressors (e.g. pancreatic hyperstimulation) develop recurrent acute pancreatitis. A subset of these patients seem to have an altered immune response that leads to accelerated fibrosis and chronic pancreatitis [19].

We hereby present four patients who seem to fit this model. Indeed, all progressed from a simple self-limited episode of acute pancreatitis to recurrent attacks, separated by completely asymptomatic disease-free periods. Within a relatively short period of time, they showed signs of chronic pancreatitis by CT criteria. There was no evidence of chronic pancreatitis during a thorough evaluation at the time of their initial attack.

Two patients underwent surgical pancreatic resection along with islet cell autotransplantation to reduce the risk and complications of pancreatogenic diabetes. This procedure was initially reported in humans in 1980 and so far, more than 150 cases have been reported [20]. The approach involves fragmentation of the pancreas, digestion of the fragmented material with collagenase, followed by centrifugation [21]. Islets cells are then cultured for several days before being transplanted. The liver remains the most common site of implantation, followed by the spleen [22].

One of the limitations of this study is the fact that the CT scan may not be sensitive enough to detect early changes of chronic pancreatitis [23, 24]. Although the initial CT scans in all four patients showed only features of acute pancreatitis, we cannot completely rule out the possibility of an acute exacerbating stage of early chronic pancreatitis in these patients.

The presented patients seem to fulfill the sentinel acute pancreatitis event hypothesis. The clinical course of these patients supports the concept that pancreatitis may be an entity with a broad spectrum of end-points ranging from an isolated episode of acute pancreatitis to chronic pancreatitis. Further studies and development of additional disease models are needed in order to fully establish this.

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