Distinct Clinical Features of Two Patients That Progressed from the Early Phase of Chronic Pancreatitis to the Advanced Phase

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Chronic pancreatitis (CP) has been considered an intractable inflammatory disease that is progressive and irreversible after definite structural changes appear in the pancreas. The Japanese diagnostic criteria for CP were revised in 2009. One of the reasons for this revision was to define a diagnostic criterion for the early phase of CP (early CP) to improve a patient’s clinical outcome, because the disease progression might be reversed in this phase by a therapeutic intervention. However, the clinical features and outcome of early CP remain largely unknown, and the diagnostic reliability of early CP needs to be verified. Here, we show two patients who met the diagnostic criteria of early CP and then progressed to the advanced, late phase of CP (definite CP). A 64-year-old man with recurrent acute pancreatitis was diagnosed as early CP and later progressed to definite CP with multiple pancreatic calcifications at the age of 69. The etiology of CP in this patient was thought to be idiopathic. The other patient was a 57-year-old man with alcohol abuse (ethanol consumption > 120 g/day). He was diagnosed as early CP and then rapidly progressed to definite CP without any acute attack. He could not remain abstinent after the diagnosis of early CP. In the present report, we retrospectively demonstrated distinct clinical features of the two patients, both of whom were diagnosed as early CP first and then progressed to definite CP. Thus, our findings support the disease concept of early CP and also suggest the validity of the revised Japanese criteria for the diagnosis of early CP.

Keywords: alcoholic chronic pancreatitis; chronic pancreatitis; early chronic pancreatitis; early stage; idiopathic chronic pancreatitis


Chronic pancreatitis (CP) is an intractable inflammatory disease recognized as a pathological state defined by chronic inflammatory changes in the pancreas resulting in the decline of the pancreatic exocrine and endocrine function, with severe fibrosis in the advanced stage. The pathological changes show an irregular and patchy distribution in the entire pancreas and are generally considered to progress irreversibly after exceeding a certain threshold (Shimosegawa et al. 2010).

The Japanese diagnostic criteria of CP were revised in 2009 (Shimosegawa et al. 2010). The revised criteria classified CP into alcoholic and nonalcoholic types from an etiological point of view, because these two types of CP followed distinct clinico-pathological courses (Chari and Singer 1994; Etemad and Whitcomb 2001; Ammann and Mullhaupt 2007). The revised criteria do not include autoimmune pancreatitis and obstructive pancreatitis in the concept of CP, but categorize them as chronic inflammation of the pancreas owing to their apparently reversible characteristics (Shimosegawa et al. 2010). The clinical diagnostic classification of CP in Japan had been divided into definite, probable and possible according to the diagnostic reliability. As definite and probable CP were defined by characteristic imaging, such as pancreatic lithiasis and severe morphological changes in the pancreatic ducts, or histological findings with or without clinical symptoms, these were already included in advanced and irreversible stages. In addition to definite, probable and possible CP, a diagnostic criterion of the early phase of CP (early CP) was newly added in the revised criteria from the standpoint of the clinical status of CP. The rationale for establishing early CP is to be able to diagnose such patients before they reach an irreversible stage of CP. It is expected that the early diagnosis of CP will contribute to improving long-term clinical outcomes.

Although the disease concept of early CP has not been fully established (Lankish 1999; Chari 2007; Mariani and Testoni 2008), it has been demonstrated that heavy alcoholic consumption is associated with pancreatic injury by alcohol-induced recurrent attacks of acute pancreatitis (AP),...
which may trigger as well as promote CP (Ammann and Mullhaupt 1994; Sata et al. 2007). On the other hand, the clinical course of nonalcoholic CP, especially in the early stage, has been less understood but was also thought to be associated with recurrent AP (Ammann and Mullhaupt 2007; Mariani and Testoni 2008).

As compared with other imaging modalities, the diagnostic usefulness of endoscopic ultrasound sonography (EUS) for early CP has been emphasized (Kahl et al. 2002; Raimondo and Wallace 2004; Irisawa et al. 2007), and its diagnostic accuracy (Catalano et al. 1998; Sahai et al. 1998) and accordance with histopathological findings (Chong et al. 2007) have been demonstrated. Moreover, the EUS-based consensus diagnostic criteria for CP, the Rosemont classification, were recently advocated (Catalano et al. 2009).

Therefore, the diagnosis of early CP requires both typical clinical features and imaging results, which are mainly obtained by EUS-based findings, in the Japanese diagnostic criteria of CP in 2009 (Shimosegawa et al. 2010). Because this is the first established specific criterion of early CP in the world, the reliability of diagnosis needs to be verified. Here, we describe the clinical courses of two patients who were first diagnosed as early CP with the Japanese criteria and showed progression to definite CP, later.

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*Patient 1:* A 64-year-old Japanese man was introduced to our department for the purpose determining the cause of recurrent AP in 2006. He suffered from the first attack of AP when he was 41 years old. He relapsed with a few mild AP attacks within two months for the first time in 23 years since the first attack. He did not have a habit of heavy drinking, but smoked 20 cigarettes per day for 44 years since he was 20 years of age. His mother died of pancreatic cancer. Physical findings were normal. Laboratory data showed elevated serum lipase but normal amylase at his first examination: serum lipase 87 U/L (normal range: 7-45 U/L), serum amylase 79 U/L (normal range: 40-126 U/L), total serum protein 7.6 g/dL (normal range: 6.5-8.2 g/dL), serum albumin 4.1 g/dL (normal range: 4.2-5.3 g/dL), serum glucose 86 mg/dL (normal range: 68-106 mg/dL) and Hb-A1c 5.6% (normal range: 4.3-5.3%). Gallbladder stones were detected by imaging examinations, while no common bile duct stone was detected. Neither pancreatic duct abnormality nor pancreatic tumor was found. There was neither calcification nor duct dilatation in the pancreas on the abdominal computed tomography (CT) (Fig. 1A, B).

![Fig. 1. Imaging results of patient 1 in 2006.](image_url)

CT revealed no abnormal findings in the pancreas head (A) and body-tail (B) of patient 1 in 2006. Hyper echoic stranding (arrow) and foci were detected in the pancreas by EUS (C). More than 3 abnormal branches are found by ERP (arrow head). However, the main pancreatic duct was not dilated (D).
Hyperechoic foci and stranding were detected by EUS (Fig. 1C). Although neither main pancreatic duct dilatation nor a protein plug was detected by endoscopic retrograde pancreatography (ERP), more than 3 branches of the pancreatic duct showed slightly irregular dilatation. These findings and his clinical features were compatible with the diagnostic criteria of early CP defined by the Japanese diagnostic criteria for CP 2009 (Shimosegawa et al. 2010). Because the concept of early CP was not established in 2006, we thought that he did not satisfy the diagnostic criteria of definite and probable CP at that time. Accordingly, he was referred back to a hospital in his hometown after our examinations. In 2008, he underwent laparoscopic cholecystectomy in accordance with his request. One year later, he suffered from mild AP again and stayed for a week in the hospital in his hometown. He had never had abdominal pain from 2006 to the last AP attack in 2009. Concomitant diabetes mellitus appeared after the last AP attack.

In 2010, we reviewed his clinical data and found that he met the criteria of the newly defined early CP. Therefore, we recommended him to undergo further examinations in our institute. His laboratory data were serum lipase 40 U/L, serum amylase 82 U/L, serum total protein 8.0 g/dL, serum albumin 4.9 g/dL, serum glucose 108 mg/dL and Hb-A1c 6.4% in 2010. Tubeless pancreatic exocrine function test, N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test, was 77.2%, which was within the normal range. Imaging results of the abdominal CT revealed multiple small calcifications in the pancreatic head (Fig. 2A), no dilatation of the main pancreatic duct and atrophy in the pancreatic body-tail compared with the findings in the CT in 2006 (Fig. 2B). EUS findings revealed pancreatic stones in the branch duct as well as pancreatic parenchyma (Fig. 2C). ERP was not performed because the patient did not agree to undergo the examination. The serine protease inhibitor Kazal type 1 (SPINK1) gene mutations, including N34S and −125T>C mutations, which had been reported to be associated with CP (Witt et al. 2000; Pfutzer et al. 2000; Kume et al. 2006), were not detected in this patient. Based on these imaging findings, he was diagnosed as definite CP this time with the Japanese diagnostic criteria for CP in 2009. In summary, a 64-year-old man,
who was once diagnosed as idiopathic early CP in 2006, progressed to definite CP in 2010 after several attacks of mild AP (Fig. 5A).

**Patient 2:** A 57-year-old Japanese man was admitted to the emergency room of our institute for diabetic ketoacidosis in 2009. His diabetes mellitus was pointed out in his thirties, but had been left untreated. After he recovered by conservative therapy, he underwent abdominal CT to examine the pancreas (Fig. 3A, B). The CT revealed a cystic lesion, 15 mm in diameter, in the pancreatic tail without any calcification nor solid tumor in the entire pancreas (Fig. 3B). Then he was introduced to our department for further examination of the cystic lesion. The EUS test revealed pancreatic cysts and an irregular pattern in the parenchyma described as lobularity without honeycombing (Fig. 3C). Magnetic resonance cholangiopancreatography (MRCP) revealed no main pancreatic duct dilatation but a cyst located in the tail (Fig. 3D). There was no finding suggesting the coexistence of pancreatic cancer. He did not agree to undergo ERP examination in his first hospital stay. He was a heavy drinker who consumed the equivalent of 60 g of pure ethanol per day from 20 to 40 years of age and 120 g per day from 40 to 57 years of age. In addition, he had smoked 20 cigarettes per day for 37 years. His laboratory data showed serum amylase 71 U/L (normal range: 40-126 U/L), serum lipase 88 U/L (normal range: 7-45 U/L), serum total protein 6.4 g/L (normal range: 6.5-8.2 g/dL), serum albumin 3.7 g/dL (normal range: 4.2-5.3 g/dL), Hb-A1c 6.6% (normal range: 4.3-5.3%), CEA 4.7 ng/mL (normal range: 0-5 ng/mL) and CA19-9 44.8 U/mL (normal range: 0-37 U/mL). Although he did not complain of abdominal pain at that time, the laboratory data of abnormal serum pancreatic enzymes, the history of heavy drinking and typical EUS findings were compatible with a diagnosis of early CP.

After discharge from our hospital, he immediately began to drink again despite several admonitions to abstain from alcohol. His pathological condition progressed rapidly from early CP to definite CP as the CT findings revealed the appearance of multiple calcifications in the pancreatic head and body 8 months later. Slight, irregular dilatation of the main pancreatic duct became obvious on the MRCP at 11 months after the discharge. Moderate dilatation and irregularity of the main pancreatic duct as well as dilatation of the pancreatic branches appeared on the MRCP taken 17 months after discharge (Fig. 4D). On the other hand, the cyst in the pancreatic tail became smaller in size on the MRCP imaging (Fig. 4D). In 2011, he was admitted again to our hospital for a mild attack of AP which was the first attack after his alcohol consumption returned to the equivalent of 120 g of pure ethanol per day. The CT imaging of the pancreas demonstrated increased numbers of
pancreatic calcifications (Fig. 4A, B) and the EUS showed many hyperechoic foci with acoustic shadows in the pancreatic head (Fig. 4C) and lobularity with honeycombing in the pancreatic body. The ERP findings showed irregular dilatation of the main pancreatic duct and branch ducts. Pancreatic exocrine function was within the normal range, 74.2% by the tubeless BT-PABA test. In short, the second case was a patient with diabetes mellitus, who drank heavily and showed rapid progress from early to definite CP within a year, apparently without associated attacks of AP (Fig. 5B).

Discussion

The previous diagnostic criteria for CP in Japan were designed to increase the diagnostic specificity. Therefore, although the criteria could diagnose relatively advanced cases as definite or probable CP (Homma et al. 1997; Otsuki 2003), the criteria could not diagnose early cases (Otsuki 2004). To improve the prognosis of patients with CP, early diagnosis is necessary because advanced CP is progressive and irreversible (Chari and Singer 1994) and the average age of death is significantly young, especially in patients with alcoholic CP (Otsuki 2003; Ammann 2006). Although the nature of early CP is currently unknown, the progression of the disease may be delayed by smoking cessation and abstinence from drinking (Gullo et al. 1988; Layer et al. 1994). In order to improve the prognosis of CP, the Japanese diagnostic criteria for CP were revised. However, as the concept of early CP is still controversial, the criteria of early CP require further confirmation.

We present two patients with different clinical backgrounds that fulfilled the criteria for early CP and then progressed to definite CP. The clinical features of these patients provide us some idea of how CP develops from normal pancreas in different etiological backgrounds. Although complete recovery from AP with only rare progress to CP had been thought to be possible, it has recently emerged that recurrent AP in patients who abuse alcohol might sometimes progress to CP according to the “necrosis-fibrosis hypothesis”, which was established based on the histological findings of AP in heavy drinkers (Kloppel and Bernard 1993; Ammann and Mullhaupt 1994). In an animal study, not only recurrent alcoholic AP but also recurrent nonalcoholic AP were shown to progress to CP, and by similar mechanisms (Matsumura et al. 2001). A sentinel acute pancreatitis event (SAPE) hypothesis, proposed by Whitcomb, demonstrated that an initial AP event would be necessary for the following development of CP (Schneider and Whitcomb 2002). This hypothesis supposes the pre-existence of risk factors (for example, alcohol, smoking and abstinence from drinking) which may trigger the disease.
Fig. 5. Clinical courses of the two patients.

A. Patient 1 suffered from the first attack of AP at 41 years of age. At 64 years of age, he suffered from the second attack. He then suffered from several attacks of AP. He was not in the habit of drinking everyday. He smoked 20 cigarettes everyday from 20 years of age. He was diagnosed as early CP when 64 years of age. After the fourth attack of AP, he was diagnosed as definite CP at 69 years of age. B. Patient 2 had a habit of heavy drinking and smoked 20 cigarettes everyday from 20 years of age. He was diagnosed as diabetes mellitus in his thirties, but the disease was untreated. He first entered a hospital for diabetic ketoacidosis at 57 years of age. He was diagnosed as early CP during his first hospital stay although he had never noticed any abdominal pain until 59 years of age. After he was discharged from his first hospital stay, he began drinking and his CP progressed rapidly. He was diagnosed as definite CP only one year later at 58 years of age. Then, he suffered from the first attack of AP at 59 years of age. yo : years old. DM : diabetes mellitus.

Fig. 6. Proposed mechanisms of developing CP in patients 1 and 2. Patient 1 fulfilled the necessary factors of the SAPE hypothesis, including a pre-existing risk factor, history of a sentinel AP event (first hit) and recurrent AP attacks and chronic stressor (second hit). On the other hand, patient 2 could not be explained by the SAPE hypothesis because there was no sentinel AP event in his clinical history. Chronic stressors, including ethanol, ethanol metabolites, nicotine and oxidative stress, might have promoted both the fibrosis in the pancreatic parenchyma and the duct abnormality in this patient.
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By EUS or ERP are required (Shimosegawa et al. 2010). The Japanese criteria of EUS findings for early CP require that more than two of the seven items are satisfied with at least one major item. The seven items of the EUS findings include 4 major features, lobularity with honeycombing, lobularity without honeycombing, hyperechoic foci without shadowing and stranding; and 3 minor features, cysts, dilated side branches and a hyperechoic duct margin (Shimosegawa et al. 2010). Because the Japanese diagnostic criteria regard the clinical features as the first selective factors for a diagnosis of early CP, the Japanese criteria require fewer and less reliable EUS findings to fulfill the criteria as compared to the Rosemont classification, which was recently proposed as the international consensus EUS-based criteria for CP (Shimosegawa et al. 2010; Catalano et al. 2009). Therefore, if a patient without any clinical features was diagnosed as early CP by EUS findings alone, the patient might be misdiagnosed.

Conclusion

In this study, we describe two patients with different clinical features who were diagnosed as early CP based on the Japanese diagnostic criteria for CP in 2009 and who then progressed to definite CP. Although the clinical features and the epidemiology of early CP are largely unknown, prospective studies need to be planned. The correct diagnosis of early CP is extremely important in the clinical setting so that a patient can be admonished to stop drinking and smoking to prevent the disease progression.

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Conflict of Interest

The authors declare no conflict of interest.

References


