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Single Case

Progression of Recurrent Pancreatitis to Chronic Pancreatitis within 3 Years due to *SPINK1* Mutation IVS3+2T>C

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Abstract
When the etiology of pancreatitis cannot be determined despite sufficient investigation, recurrence and progression to chronic pancreatitis often involve genetic mutations. Herein, we describe a case of recurrent pancreatitis with the IVS3+2T>C mutation in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene that progressed to chronic pancreatitis in only 3 years. A 35-year-old man was referred to our hospital, where he was diagnosed with mild pancreatitis and was treated conservatively. However, the patient experienced recurrent episodes of pancreatitis, which progressed to become chronic pancreatitis with a pancreatic calcification 1 year later. After 3 years, the patient developed pancreatic duct stenosis and required a pancreatic duct stent placement. Regarding the cause of chronic pancreatitis, alcohol abuse was ruled out based on history taking. Considering the course of treatment, autoimmune pancreatitis and obstructive pancreatitis, such as pancreatic divisum, were also ruled out. Finally, a germline genetic test was performed to determine the etiology of pancreatitis, which revealed the IVS3+2T>C mutation in *SPINK1*. This case shows the importance of genetic testing in patients with idiopathic pancreatitis to determine their etiology and is a rare incident that can report the progression of the disease from acute to chronic pancreatitis.

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Introduction

Idiopathic pancreatitis (IP) is defined as pancreatitis without a definitive cause despite sufficient investigation and is the second most common etiology of pancreatitis after alcohol [1]. Jalaly et al. [2] reported that among those diagnosed with IP, gene alterations in either *PRSS1*, *CFTR*, *SPINK*, or *CTRC* occurred in 47.8% of patients, especially among those aged <35 years. *SPINK1* is synthesized in pancreatic acinar cells and secreted in the pancreatic juice. *SPINK1* binds to trypsin and inhibits its active site, which reduces the total trypsin activity by 20% and acts as a primary defense system to protect the pancreas from autolysis.

The relationship between *SPINK1* mutations and pancreatitis has been reported, but only a few studies have traced the course of pancreatitis from its onset to becoming chronic [3]. In this case report, we discuss our experience with a case of recurrent pancreatitis due to a *SPINK1* mutation that progressed to chronic pancreatitis.

Case Presentation

A 35-year-old man visited a hospital complaining of abdominal pain 3 years ago. He was 175 cm tall, weighed 50 kg, and had no physical findings of note other than tenderness at the pericardial fossa. He had no history of smoking and no family history of pancreatic disease. His alcohol consumption was 20 g per day. The laboratory test results showed a mildly elevated C-reactive protein level (4.04 mg/dL) and elevated pancreatic enzyme levels (pancreatic amylase: 67 U/L; lipase: 163 IU/L). His hepatobiliary enzyme, bilirubin, and immunoglobulin G4 levels were normal. Regarding tumor markers, elastase-I was elevated (679.6 ng/dL), but levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal ranges. The Pancreatic Functioning Diagnostant (PFD) test revealed a normal pancreatic exocrine function (PFD excretion rate: 71.6%). Initially, he was diagnosed with mild pancreatitis due to alcohol abuse, which improved with conservative treatment. The patient was followed up and advised to modify his lifestyle and to discontinue consuming alcohol; however, symptoms of pancreatitis recurred. He was suspected of having recurrent IP and was referred to our hospital for further examination.

Computed tomography (CT) showed no obvious findings of chronic pancreatitis (shown in Fig. 1a). However, endoscopic ultrasound (EUS), which was performed to determine the etiology of the patient's pancreatitis, revealed both the hyperechoic foci with posterior acoustic shadow and the honeycomb pattern of lobularity, which are considered EUS findings of chronic pancreatitis by the Rosemont classification (shown in Fig. 1b) [4]. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography showed that the pancreatic duct was narrowed in several locations (skip lesions), but no obstruction was found (shown in Fig. 1c, d). Although we did not completely evaluate whether the bile ducts were narrowed by chronic pancreatitis, there was no evidence of hepatic dysfunction or jaundice. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography findings showed irregular dilation of the main and branch pancreatic ducts. These were probable findings of chronic pancreatitis in the Japanese Chronic Pancreatitis Diagnostic Criteria 2019 [1]. The patient in this case was diagnosed with definitive disease at the first visit to our hospital owing to the imaging findings of probable chronic pancreatitis, repeated abdominal pain, and abnormal pancreatic enzyme levels. However, the cause of pancreatitis remained unresolved. Through imaging studies, autoimmune pancreatitis was suspected; however, the patient's overall condition and laboratory results did not meet the diagnostic criteria. We also performed fine needle aspiration of the pancreas for pathological diagnosis of autoimmune pancreatitis, but no pathological findings

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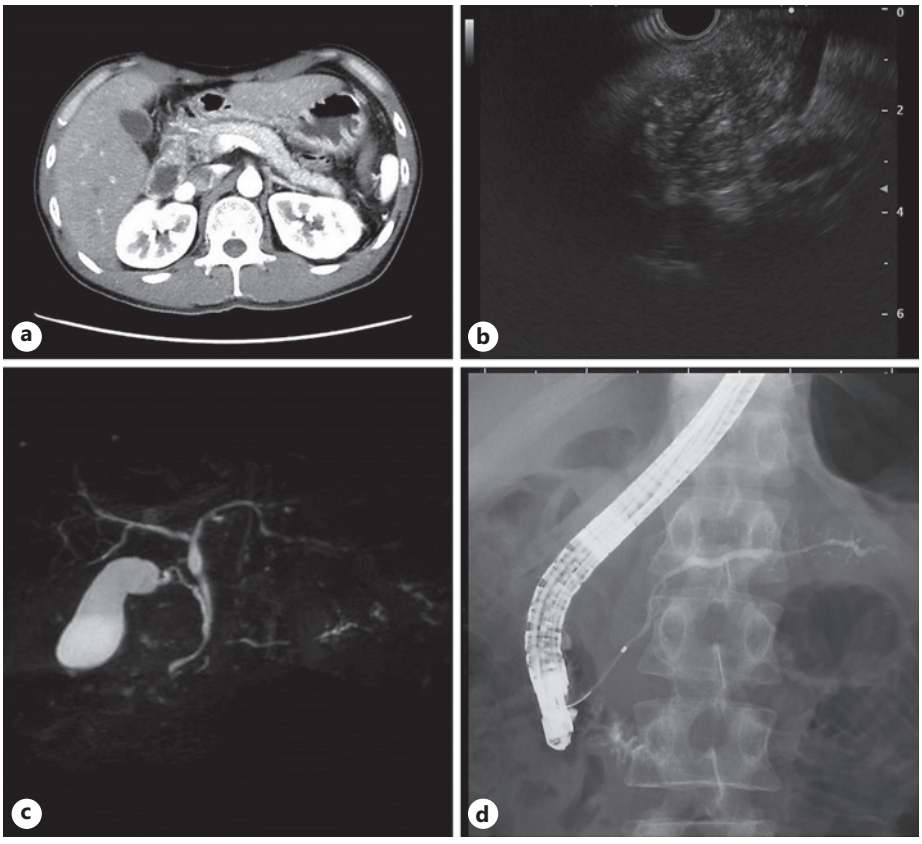

Fig. 1. Imaging findings at initial examination. **a** Contrast CT shows no apparent pancreatic abnormality. **b** Endoscopic ultrasound shows both hyperechoic foci with posterior acoustic shadow and a honeycomb pattern of lobularity, which are considered EUS findings of chronic pancreatitis by the Rosemont classification. **c** Magnetic resonance cholangiopancreatography shows narrowing of the pancreatic duct in two locations. **d** Endoscopic retrograde cholangiopancreatography also shows irregular dilation of the main pancreatic duct and branch pancreatic ducts.

specific for autoimmune pancreatitis were obtained. In addition, fine needle aspiration revealed mild fibrosis of the pancreatic tissue, although the sample volume was limited. On the other hand, no malignant findings were found. Hence, a steroid trial was performed, which did not improve the patient's condition.

He was repeatedly reexamined over the next 3 years, during which time he continued to experience recurrences of pancreatitis. One year after his initial visit to our hospital, a pancreatic calcification developed in the pancreatic head (shown in Fig. 2a). Two years later, new dilatations in the main pancreatic duct were observed (shown in Fig. 2b). Three years later, recurrences of pancreatitis became more frequent. CT showed diffuse calcifications in the pancreas and further dilatation of the main pancreatic duct (shown in Fig. 2c).

As a pancreatic duct stenosis in the pancreatic head was presumed to be the cause of the increased frequency of recurrences, a pancreatic duct drainage procedure was performed. As the duct of Wirsung at the pancreatic head had become stenosed and was filled with calcifications, drainage from the duct of Wirsung was difficult. Ultimately, drainage of the pancreatic body and tail was achieved through the accessory papilla (shown in Fig. 3a–c).

Over the same 3-year period, repeated cytological examinations were performed due to the pancreatic duct stenosis, but no findings of malignancy were found. Since the cause of the rapid progression to established chronic pancreatitis after a relatively short period (3 years)

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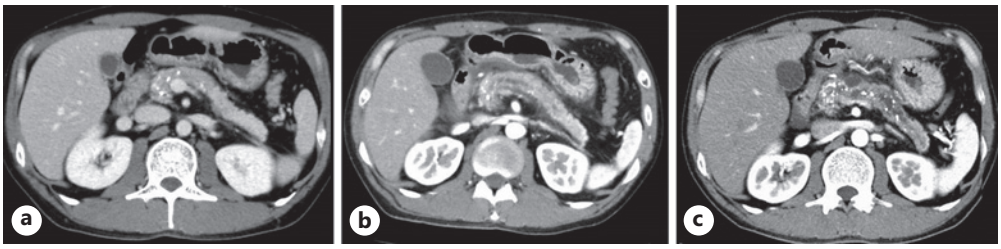

Fig. 2. Changes in CT findings over time. **a** One year later, CT also shows diffuse calcification of the pancreatic parenchyma. **b** Two years later, in addition to diffuse calcification, pancreatic duct dilatation became prominent. **c** Three years later, more calcification of the pancreas. Calcification is also seen within the main pancreatic duct, and duct dilatation has become stronger.

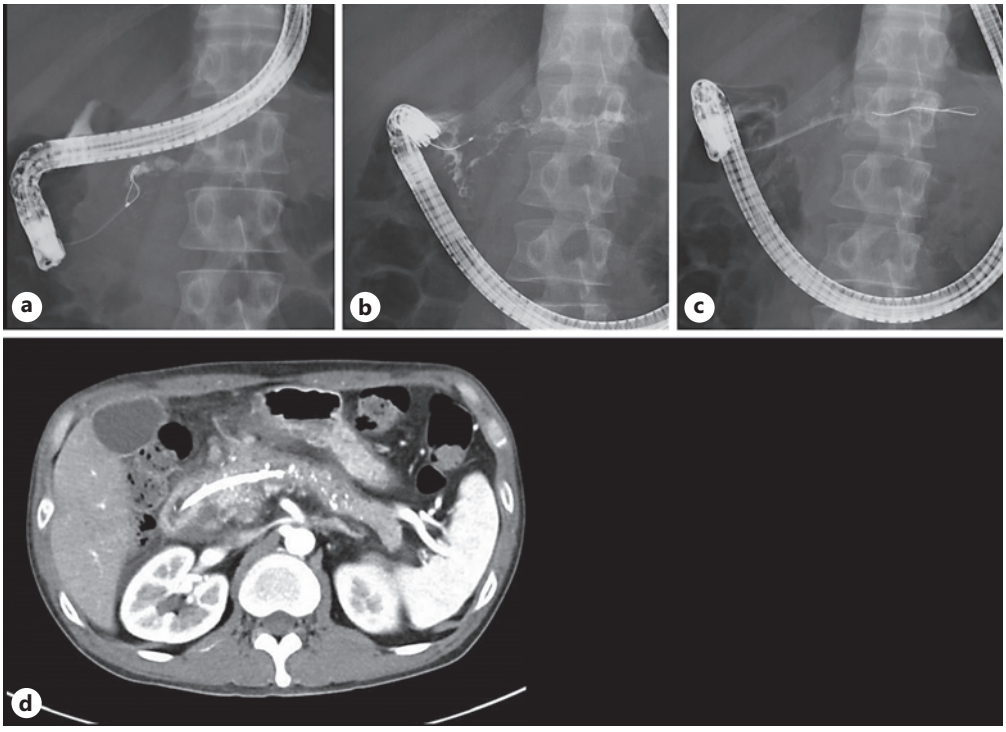

Fig. 3. Pancreatic duct stenting for a pancreatic duct stenosis in the pancreatic head. **a** The Wirsung duct is obstructed by a pancreatic stone. For this reason, stent placement through the Wirsung duct had to be abandoned. **b** The accessory papilla approach is used. **c** The pancreatic duct stent is placed from the accessory papilla to the main pancreatic duct. **d** The pancreatic duct dilation at the pancreatic tail is improved by pancreatic duct stenting.

remained unclear, we attempted to investigate a genetic etiology. Although his family history was negative for pancreatitis, next-generation sequencing revealed a mutation in *SPINK1* (IVS3+2T>C) (described in the online suppl. Material; for all online suppl. material, see www.karger.com/doi/10.1159/000528768). Currently, the patient undergoes stent replacement every 3 months. No recurrence of acute or chronic pancreatitis has been reported for more than 6 months since the first pancreatic duct stent was placed (Fig. 3d). Over the course of approximately 3 years, the patient did not show any worsening of glucose intolerance. As for exocrine function, there were no obvious clinical symptoms, such as fatty stools, but the serum

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pancreatic enzyme level decreased over time. PFD test values were normal, but serum pancreatic enzymes gradually became abnormally low during the course of the disease, and pancreatic enzyme replacement therapy was initiated due to the presence of epigastric discomfort possibly caused by the pancreas.

The patient is regularly monitored and surveilled for an early detection of pancreatic cancer. At our institution, we observe patients every 3 months and perform blood tests and CT/MRI or EUS every 6 months on an exploratory basis.

Conclusion

Herein, we present a case of a patient with recurrent pancreatitis due to a *SPINK1* (IVS3+2T>C) mutation. Although several reports have mentioned the usual age at which patients with pancreatitis caused by genetic mutations develop chronic pancreatitis, reports that have been able to follow the progression of the disease are rare. The natural history of *SPINK1*-related pancreatitis is currently not well described, and previous literature reports remain controversial. In previous reports, the cumulative incidence of CP symptoms was 16.1% at 20 years, 38.5% at 30 years, 56.7% at 40 years, and 76.0% at 50 years. *SPINK1*-associated pancreatitis was associated with an earlier onset of pancreatic inflammation. The risk of pancreatic cancer was 12 times that of IP. Median age at symptom onset was 20.1 (17.5–22.8) years in the *SPINK1* group. The median delay between the first symptoms and the diagnosis of CP was 6.9 years (95% CI, 4.5–9.3) [3]. Compared with patients with IP, patients in the *SPINK1*-associated pancreatitis group had more episodes of acute pancreatitis, more pancreatic pain, and more frequent and earlier morphological signs of CP. In addition, they were at significantly higher risk of developing chronic pancreatitis. In this case, although the onset of acute pancreatitis was slightly during the older age, the patient transitioned to established chronic pancreatitis at an earlier course than previously reported. It is assumed that most of the previously reported *SPINK1*-associated pancreatitis will be heavily influenced by the most well-studied variants. Accumulation of cases will reveal whether each *SPINK1* variant associated with pancreatitis has a unique phenotype.

In this case, an endoscopic stent placement for the stenosis of the dominant pancreatic duct was successful in preventing recurrent pancreatitis. Long-term repetitive endoscopic treatment of chronic pancreatitis has not been fully evaluated, and currently, surgical treatment is believed to be superior in terms of pain control. However, stenting is often the initial treatment of choice due to its less invasive nature and fewer complications. Repeated endoscopic treatment for pain relief over a long period of time (several years or more) should be avoided. Although this is a case of hereditary pancreatitis, a previous report showed no difference in the rate of surgical conversion between *SPINK1* pancreatitis and other IP, and we assume that the same treatment strategy is generally applicable [3].

The mechanistic definition of chronic pancreatitis showed that focusing too much on the abnormal morphology of chronic pancreatitis sometimes can make early diagnosis difficult [5]. Chronic pancreatitis can be viewed as a continuum of concepts: at risk, acute and recurrent pancreatitis, early chronic pancreatitis, established chronic pancreatitis, and end-stage chronic pancreatitis. In this case, a patient with a genetic predisposition to “at risk” was followed up on the process leading to established chronic pancreatitis. Chronic pancreatitis is a progressive process that is fraught with problems, such as atrophy of the pancreas, fibrosis of the pancreas, pain, narrowing of the pancreatic duct, calcification, exocrine disorders, endocrine disorders, and carcinogenesis as atypia, each of which requires a categorical approach for early diagnosis.

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While exon 3 of *SPINK1* encodes a trypsin-binding site, the IVS3+2T>C mutation causes splicing abnormalities that lead to the deletion of exon 3 [6]. This, in turn, downgrades the suppression of trypsin, which causes pancreatitis. Witt et al. reported that 22 of 96 young patients with chronic pancreatitis had *SPINK1* mutation [7]. Genetic risk factors may vary based on regional and racial differences; the IVS3+2T>C mutations of *SPINK1* have been strongly associated with idiopathic chronic pancreatitis in East Asia [8]. American College of Gastroenterology Guidelines recommend *PRSS1*, *SPINK1*, *CFTR*, and *CTRC* gene testing, especially in young patients with chronic pancreatitis of unknown etiology [4]. In Japan, the *PRSS1* and *SPINK1* genes are used as diagnostic criteria for early-stage chronic pancreatitis and are becoming increasingly important in daily medical practice. However, the insurance does not cover these genes, and genetic testing for pancreatitis has thus far been performed only at a limited number of institutions for research purposes.

The natural history of *SPINK1*-associated pancreatitis has not yet been fully reported, and in this case, recurrent pancreatitis rapidly progressed to become chronic, eventually requiring an endoscopic intervention. In cases of a relatively young patient with recurrent pancreatitis of unclear cause, genetic testing should be considered to determine the etiology of the disease. The CARE Checklist has been completed by the authors for this case report and attached as online supplementary material.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and approved by the Ethics Committee of the Kobe University School of Medicine, approval number B190114.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Susumu Horitani and Masahiro Tsujimae wrote the manuscript together with Arata Sakai; Atsuhiro Masuda, Kae Nagao, Shinya Kohashi, Noriko Inomata, Hisahiro Uemura, Shigeto Masuda, Masanori Gonda, Shohei Abe, Kohei Yamakawa, Shigeto Ashina, Yasutaka Yamada, Takeshi Tanaka, Ryota Nakano, Takashi Kobayashi, and Hideyuki Shiomi reviewed the manuscript and collected the data; Yuzo Kodama supervised the study and revised the manuscript accordingly.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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