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Contents

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EDITORIAL

- 1382 Latest updates on structure and recommendations of cardiac rehabilitation programs in chronic heart failure
Kourek C, Briasoulis A, Magouliotis DE, Skoularigis J, Xanthopoulos A
- 1388 Immunoglobulin A glomerulonephropathy: A review
El Labban M, Surani S

ORIGINAL ARTICLE

Retrospective Study

- 1395 Serum proteins differentially expressed in gestational diabetes mellitus assessed using isobaric tag for relative and absolute quantitation proteomics
Cao WL, Yu CP, Zhang LL

Observational Study

- 1406 Effect of comprehensive nursing on the quality of life and swallowing function in individuals diagnosed with ischemic stroke
Hu HF, Sang YF, Xiao YQ

META-ANALYSIS

- 1416 Safety and effectiveness of butorphanol in epidural labor analgesia: A protocol for a systematic review and meta-analysis
Tang GC, He M, Huang ZZ, Cheng Y

CASE REPORT

- 1422 Left lower lobe sleeve resection for the clear cell variant of pulmonary mucoepidermoid carcinoma: A case report
Yu XH, Wang WX, Yang DS, Gong LH
- 1430 Lower extremity peripherally inserted central catheter placement ectopic to the ascending lumbar vein: A case report
Zhu XJ, Zhao L, Peng N, Luo JM, Liu SX
- 1437 Effect of foot reflexology on an infant with sensorineural hearing loss: A case report
Lee YJ, Chen MQ, Dong J
- 1442 Development of immature ovarian teratoma after mature teratoma in a girl with familial ovarian teratoma: A case report
Ju UC, Kang WD, Kim SM

- 1448** Metastatic clear cell sarcoma of the pancreas: A rare case report
Liu YJ, Zou C, Wu YY
- 1454** 3M syndrome patient with a novel mutation: A case report
Luo MR, Dai SM, Li Y, Wang Q, Liu H, Gao P, Liu JY, Chen J, Zhao SJ, Yin GY
- 1461** Appendiceal intussusception complicated by adenocarcinoma of the cecum: A case report
Long Y, Xiang YN, Huang F, Xu L, Li XY, Zhen YH
- 1467** Malignant triton tumor in the abdominal wall: A case report
Yang HJ, Kim D, Lee WS, Oh SH
- 1474** Multilocular thymic cysts can be easily misdiagnosed as malignant tumor on computer tomography: A case report
Sun J, Yang QN, Guo Y, Zeng P, Ma LY, Kong LW, Zhao BY, Li CM
- 1481** Diagnosis of poorly differentiated adenocarcinoma of the stomach by confocal laser endomicroscopy: A case report
Lou JX, Wu Y, Huhe M, Zhang JJ, Jia DW, Jiang ZY
- 1487** High-grade pancreatic intraepithelial neoplasia diagnosed based on changes in magnetic resonance cholangiopancreatography findings: A case report
Furuya N, Yamaguchi A, Kato N, Sugata S, Hamada T, Mizumoto T, Tamaru Y, Kusunoki R, Kuwai T, Kouno H, Kuraoka K, Shibata Y, Tazuma S, Sudo T, Kohno H, Oka S
- 1497** Chronic infectious unilateral giant thyroid cyst related to diabetes mellitus: A case report
Liu JB, Zhang SL, Jiang WL, Sun HK, Yang HC
- 1504** Multiple thoracic and abdominal foregut duplication cysts: A case report
Alsinan TA, Altokhais TI
- 1510** Advanced cervix cancer patient with chemotherapy-induced grade IV myelosuppression achieved complete remission with cadonilimab: A case report
Zhu R, Chen TZ, Sun MT, Zhu CR
- 1517** Detection of 4p16.3 deletion and 11p15.5p15.4 gain in a boy by comparative genomic hybridization array: A case report
Kaya I
- 1523** Eccrine porocarcinoma in the temple of an elderly woman: A case report
Wu ZW, Zhu WJ, Huang S, Tan Q, You C, Hu DG, Li LN
- 1530** Analysis and monitoring of drug therapy in a patient with peptic ulcer complicated by infection: A case report
Gou YP, Huang Y, Chen L, Zheng W, Zheng YH
- 1536** Primary gastroduodenal tuberculosis presenting as gastric outlet obstruction: A case report and review of literature
Ali AM, Mohamed YG, Mohamud AA, Mohamed AN, Ahmed MR, Abdullahi IM, Saydam T

- 1544** Clinical manifestations and the prenatal diagnosis of trisomy 7 mosaicism: Two case reports

Hou F, Li Y, Jin H

ABOUT COVER

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High-grade pancreatic intraepithelial neoplasia diagnosed based on changes in magnetic resonance cholangiopancreatography findings: A case report

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Abstract

BACKGROUND

High-grade pancreatic intraepithelial neoplasia (PanIN) exhibits no mass and is not detected by any examination modalities. However, it can be diagnosed by pancreatic juice cytology from indirect findings. Most previous cases were diagnosed based on findings of a focal stricture of the main pancreatic duct (MPD) and caudal MPD dilatation and subsequent pancreatic juice cytology using endoscopic retrograde cholangiopancreatography (ERCP). We experienced a case of high-grade PanIN with an unclear MPD over a 20-mm range, but without caudal MPD dilatation on magnetic resonance cholangiopancreatography (MRCP).

CASE SUMMARY

A 60-year-old female patient underwent computed tomography for a follow-up of

uterine cancer post-excision, which revealed pancreatic cysts. MRCP revealed an unclear MPD of the pancreatic body at a 20-mm length without caudal MPD dilatation. Thus, course observation was performed. After 24 mo, MRCP revealed an increased caudal MPD caliber and a larger pancreatic cyst. We performed ERCP and detected atypical cells suspected of adenocarcinoma by serial pancreatic juice aspiration cytology examination. We performed a distal pancreatectomy and obtained a histopathological diagnosis of high-grade PanIN. Pancreatic parenchyma invasion was not observed, and curative resection was achieved.

CONCLUSION

High-grade Pan-IN may cause MPD narrowing in a long range without caudal MPD dilatation.

Key Words: Pancreatic cancer; Pancreatic intraepithelial neoplasm; High-grade pancreatic intraepithelial neoplasm; Magnetic resonance cholangiopancreatography; Carcinoma *in situ*; Case report

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Core Tip: High-grade pancreatic intraepithelial neoplasia (PanIN) is diagnosed using pancreatic juice cytology. Most reasons for performing endoscopic retrograde cholangiopancreatography (ERCP) are focal main pancreatic duct (MPD) stenosis and/or caudal MPD dilatation. Poor MPD depiction without caudal MPD dilatation on magnetic resonance cholangiopancreatography sometimes occurs in normal individuals. Thus, we hesitate to send these patients to undergo ERCP. As such, course observation is necessary to confirm whether or not caudal MPD dilatation and/or cyst formation develop(s). Accordingly, it is better to submit the patient to ERCP to detect high-grade PanIN if caudal MPD dilatation and/or cyst formation occur(s).

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INTRODUCTION

High-grade pancreatic intraepithelial neoplasia (PanIN) grows in the pancreatic duct with flat or low-papillary progression and is included in pancreatic cancer (PC) stage 0. Thus, high-grade PanIN is considered a curable PC, and attention has been paid to its diagnosis. Unfortunately, PanIN does not form a mass and can only be diagnosed by pancreatic juice cytology from indirect findings [e.g., main pancreatic duct (MPD) stricture and dilatation, pancreatic cyst, and pancreatic atrophy]. Most cases are characterized by limited MPD stenosis following caudal MPD dilatation. Herein, we report a case of high-grade PanIN that demonstrated a poor description of the MPD in a rather long range, with no caudal MPD dilatation.

CASE PRESENTATION

History of present illness

A 60-year-old female patient underwent a computed tomography scan for a follow-up of uterine cancer post-excision, which revealed pancreatic cysts.

History of past illness

The patient had diabetes mellitus and did not smoke or drink alcohol.

Personal and family history

The patient had no family history of PC or chronic pancreatitis.

Physical examination

Physical examination on admission indicated a height of 156 cm, weight of 68.5 kg, and body mass index of 27.4 kg/mm². Her abdomen was soft and flat with no palpable mass.

Laboratory examinations

The patient's relevant laboratory data included hemoglobin A1c of 11.8% and CA19-9 of 57 U/mL.

Imaging examinations

Contrast-enhanced computed tomography (CE-CT) revealed a 5-mm round cyst in the pancreatic tail but with no solid mass, atrophy, or fatty change in the pancreas (Figure 1). Further, endoscopic ultrasonography (EUS) revealed a diffuse high echoic spot in the whole pancreas (Figure 2A and B), indicating early chronic pancreatitis and a small round cyst in the pancreatic tail (Figure 2C), and there was no caudal MPD dilatation (Figure 2D). A solid mass, hypoechoic area around the MPD, or caudal MPD dilation was not detected. Magnetic resonance cholangiopancreatography (MRCP) poorly described the MPD at the 20-mm length of the pancreatic body/tail (Figure 3A), with no caudal MPD dilation. This finding appeared like irregular MPD narrowing in other MRCP sequences (Figure 3B). Imaging examination for pancreatic cysts was followed up twice a year. MPD findings indicated no changes after 6 mo (Figure 4A and B). The range of MPD narrowing did not change over 24 mo, but caudal MPD dilatation was slightly detected and the cyst size had increased (Figure 4C and D).

FURTHER DIAGNOSTIC WORKUP

We performed a further examination considering the induction of high-grade PanIN. CE-CT revealed no solid space-occupying lesion, including a delayed enhanced area, but the pancreatic tail cyst grew to 10 mm, and the caudal MPD was slightly dilated (Figures 5). On EUS, the cyst was described as a solid mass (Figure 6A), but contrast-enhanced EUS using Sonazoid showed the mass as a round cystic lesion (Figure 6B). On CT, MRCP, and EUS, we could not find a connection between MPD and the cyst. Endoscopic retrograde cholangiopancreatography (ERCP) revealed that the MPD in the pancreatic tail was irregularly narrowing over a 20-mm range and caudal MPD was slightly dilated (Figure 7A). Serial pancreatic juice aspiration cytology examination (SPACE) revealed adenocarcinomas in three out of four samples (Figure 7B). Whole body CE-CT, positron emission tomography, and magnetic resonance imaging with gadoxetate sodium revealed no PC metastasis.

FINAL DIAGNOSIS

The patient was diagnosed with high-grade PanIN.

TREATMENT

A distal pancreatectomy was performed.

OUTCOME AND FOLLOW-UP

Surgical results included a 10-mm round cyst located in the pancreatic tail and a low-papillary adenocarcinoma (Figure 8A and B) that spread in the cyst wall. Cancer cells had spread to the MPD and branch duct (BD), over a 20-mm range toward the pancreatic body (Figure 8C). Pancreatic parenchyma invasion was not observed, and the final diagnosis of her tumor was high-grade PanIN. The samples demonstrated some low-grade PanINs in the pancreas, with few fibrotic areas around the MPD with high-grade PanIN. Figure 8D shows the distribution of PanIN. The patient was alive without relapse 17 months postoperatively.

DISCUSSION

We experienced a case of high-grade PanIN, which was effectively diagnosed by course observation with MRCP. Cyst growth and caudal MPD dilatation enabled the SPACE. PC has high malignancy and is frequently detected in progressive situations. Thus, PC is the worst prognostic cancer, with a 5-year survival rate of approximately 7.1% and 10% in Japan and the United States, respectively[1,2]. PanIN is a tumor that develops in a flat or low papillary shape within the pancreatic duct, with highly atypical cases classified as high-grade PanIN and included in PC stage 0. Thus, many physicians have been exerting an effort to detect stage 0 PC. However, the proportion of stages 0 and 1A cases accounted for only 1.7% and 4.1%, respectively[3,4]. High-grade PanIN does not form a mass, and imaging modalities cannot identify the carcinoma; therefore, recently, stage 0 has been diagnosed using pancreatic juice cytology[5,6], focusing on indirect findings, including MPD dilatation and/or stenosis, cyst formation, and focal atrophy of the pancreas[4,7-9]. Fibrosis around the MPD from obstructive pancreatitis by high-grade PanIN or immunological reaction for PanIN was believed to induce MPD stenosis[10].

Clear pancreatic duct stenosis or caudal MPD dilatation detected with any imaging modalities warrants readily recommending a trial of endoscopic retrograde pancreatography (ERP) cytology to the patient. However, the poor delineation of the MPD at relatively long distances by MRCP is a finding observed in normal cases. Pancreatic duct stenosis is frequently detected using MRCP, but which finding should be used to perform ERCP seems to be a problem,

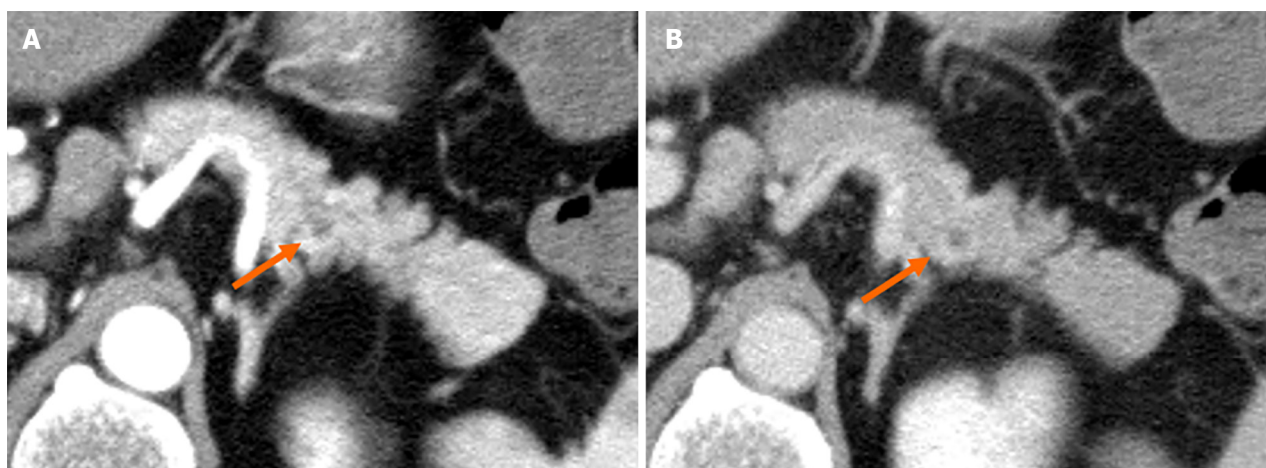


Figure 1 Computed tomography revealed a 5-mm round cyst in the pancreatic tail (arrow) but with no solid mass, atrophy, or fatty change in the pancreas. A: Pancreatic parenchymal phase; B: Equilibrium phase.

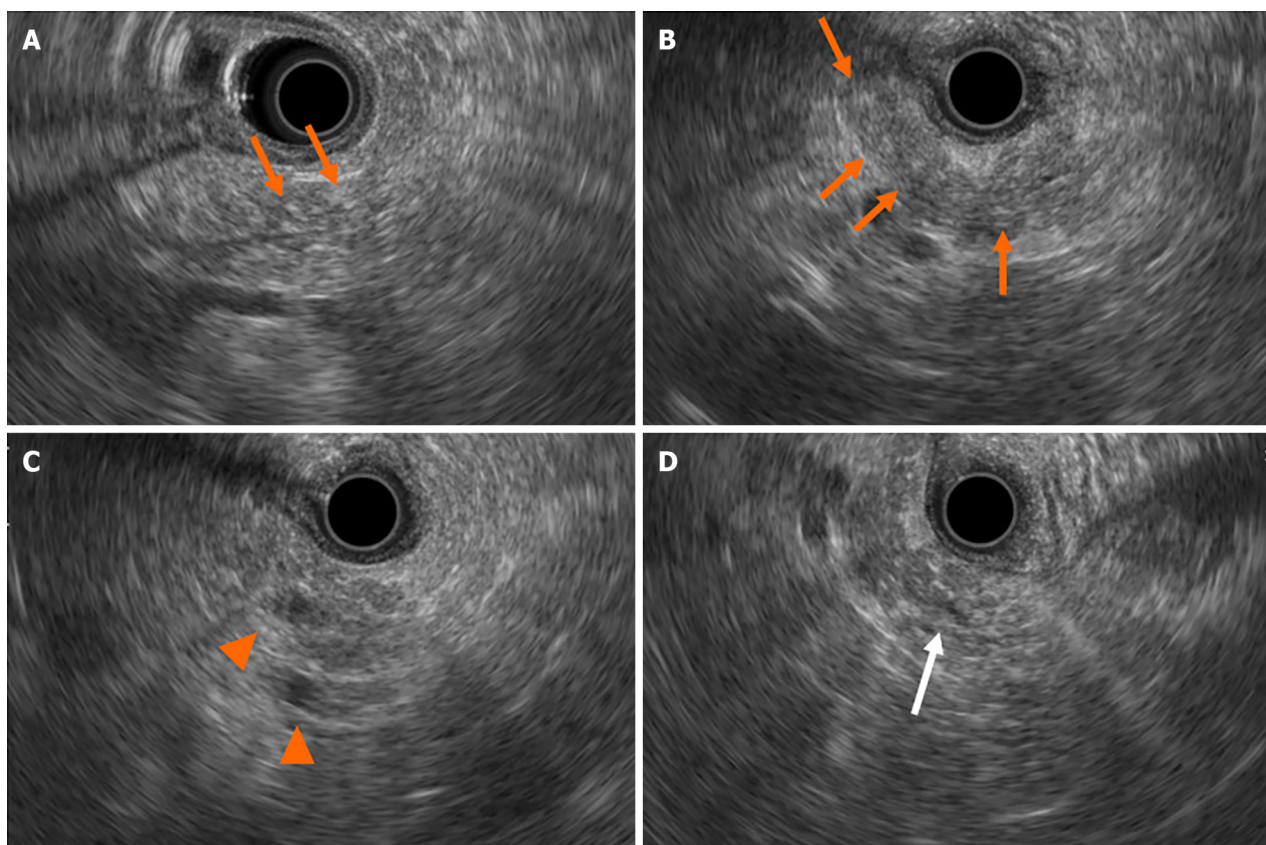


Figure 2 Findings of endoscopic ultrasonography at first visit to our institute. A and B: There were diffuse high echoic spots (orange arrows) in the whole pancreas, indicating early chronic pancreatitis; C: Small round cysts (arrowheads) were found in the pancreatic tail; D: There was no caudal main pancreatic duct dilatation in the pancreatic tail (white arrow).

which is fraught with the risk of acute pancreatitis.

In recent years, Hanada *et al*[11] classified high-grade PanIN based on histopathological features. It is categorized into a flat type, in which mainly the flat tumor cells are limited to the BD, and a low papillary type, in which the low papillary tumor cells spread over a long distance from the BD to the MPD. Thus, the reason for MPD stenosis in the flat type is frequently induced by fibrosis around the tumor and the flat type might demonstrate a short length of stenosis and strong caudal MPD dilatation. In comparison to the flat type, the low papillary type induces MPD stenosis by both tumor progression in the MPD and fibrosis around the tumor. Thus, the length of stenosis can be longer than that associated with a flat type due to tumor progression in the MPD. Additionally, the stenosis might be milder in the low papillary type than in the flat type if the low papillary type demonstrates little fibrosis around the tumor. In our case, low papillary progression and little fibrosis around the MPD might have reduced MPD stenosis and caudal MPD dilatation at the first

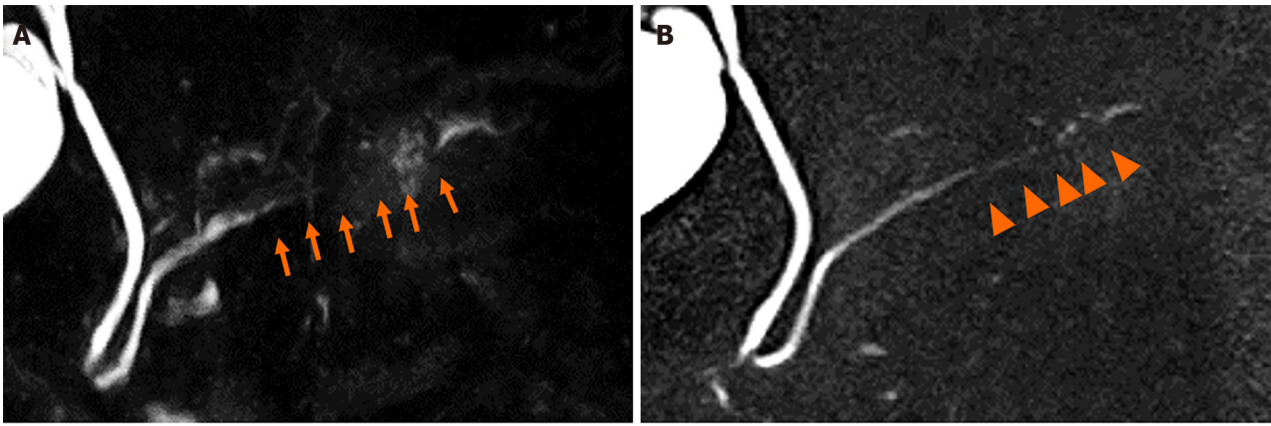


Figure 3 Findings of magnetic resonance cholangiopancreatography at first visit to our institute. A: The main pancreatic duct (MPD) had poor description in a 20-mm range (arrows) at the pancreatic body/tail, but there was no dilation of the caudal MPD; B: Other sequence of magnetic resonance cholangiopancreatography revealed irregular MPD in the same position (arrowheads).

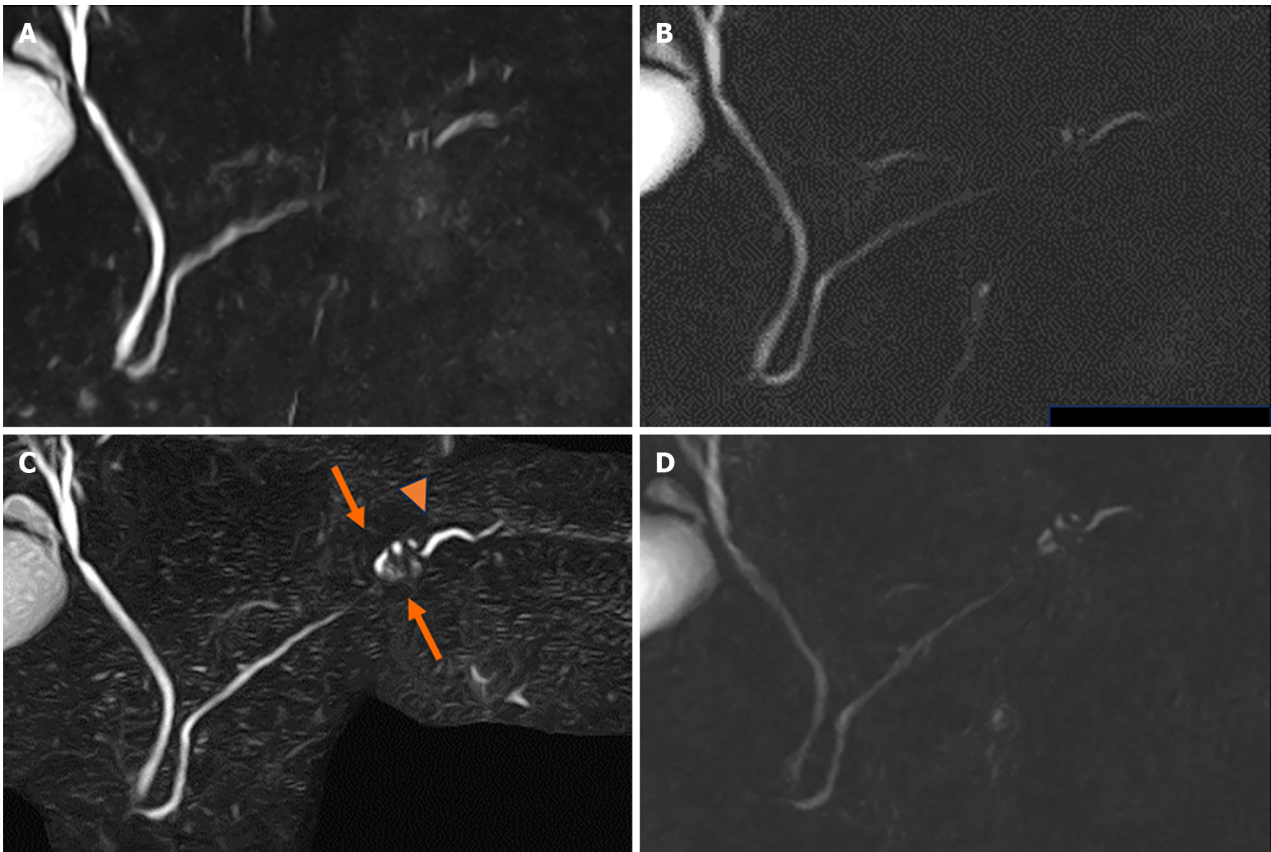


Figure 4 Changes of magnetic resonance cholangiopancreatography findings. A: Magnetic resonance cholangiopancreatography (MRCP) findings demonstrated no change at 6 months; B: Other MRCP sequence at 6 months; C: Caudal cyst has grown (arrows) and caudal main pancreatic duct caliber has slightly increased (arrowhead) at 24 months; D: Other MRCP sequence at 24 months.

visit.

We collected and performed a review of previous relevant reports. We searched PubMed and Ichushi-web (Japanese) from 2012 to 2022 for cases of high-grade PanIN with detailed information on MRCP and histopathological findings (Table 1). We found 27 cases[8,12-34], including 9 head lesions, 10 body lesions, and 8 tail lesions. Compared to the usual PC, involvement of the body and tail tended to be more frequent. Of the 27 cases, MPD stenosis was observed in 24 cases. Further, all MPD stenosis, caudal MPD dilatation, and caudal cyst findings were present in 13 cases. Notably, not only the caliber of the MPD, but also the caudal cyst, which is a dilated BD, is an important finding in the search for high-grade PanIN. Based on histopathological findings, in 24 cases we found that the cause of MPD stenosis was fibrosis around the MPD. Fibrosis around the stricture and carcinoma *in situ* proliferation contributed to pancreatic duct stricture in 15 cases, and in four cases it was due to fibrosis alone. Five cases demonstrated almost no fibrosis, and the stenosis may have been

Table 1 Magnetic resonance cholangiopancreatography findings and causes of main pancreatic duct stenosis in high-grade pancreatic intraepithelial neoplasia

Case number	27
Sex (M:F)	17:10
Age (yr), median (range)	74 (60-83)
Localization of tumor	
Head:body:tail	9:10:8
MRCP findings	
MPD stenosis	3
MPD stenosis + caudal MPD dilatation	5
MPD stenosis + caudal MPD dilatation + caudal cyst formation	13
Caudal cyst formation	2
Others	4
MPD stenosis, yes:no	24:3
Histological type ¹	
Flat type:low papillary type	6:21
Distribution of tumor	
MPD:BD:MPD + BD	10:5:12
Causes of MPD stenosis	
Fibrosis around MPD	4
Tumor itself	5
Fibrosis around MPD + tumor itself	15

¹Histological type of tumor was decided by Hanada’s classification[7].
M: Male; F: Female; MRCP: Magnetic resonance cholangiopancreatography; MPD: Main pancreatic duct; BD: Branch duct.

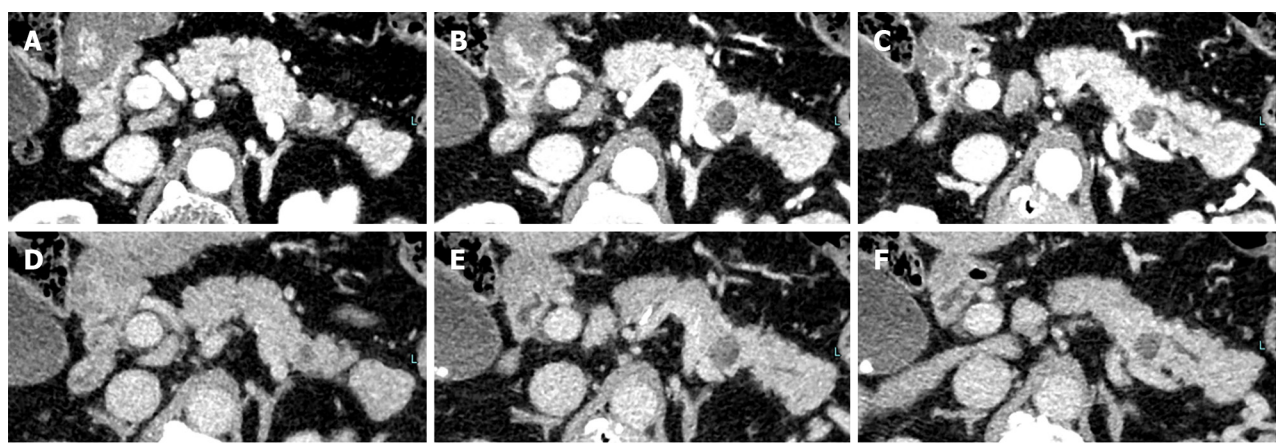


Figure 5 Computed tomography at 24 months revealed no solid space-occupying lesion but the pancreatic tail cyst has grown to 10 mm and the caudal main pancreatic duct was slightly dilated. A-C: Pancreatic parenchymal phase; D-F: Equilibrium phase.

caused by the tumor tissue itself. Fibrosis around the pancreatic duct was considered a major factor in stenosis. Among the 21 patients with the low papillary type, 13 demonstrated both fibrosis and carcinoma *in situ* proliferation in the stenosis area, and four exhibited only fibrosis, indicating the frequent involvement of stenosis. Only three cases were caused by the growth of carcinoma *in situ*.

In this case, the cyst expansion over time and the caudal MPD dilatation triggered the discovery of PanIN. Further, the MPD stenosis was thought to be caused by the progression of tumor cells because the tumor tissue was low-papillary and almost no fibrosis was observed in the stenotic part. Papillary hyperplasia may have progressed along the pancreatic duct

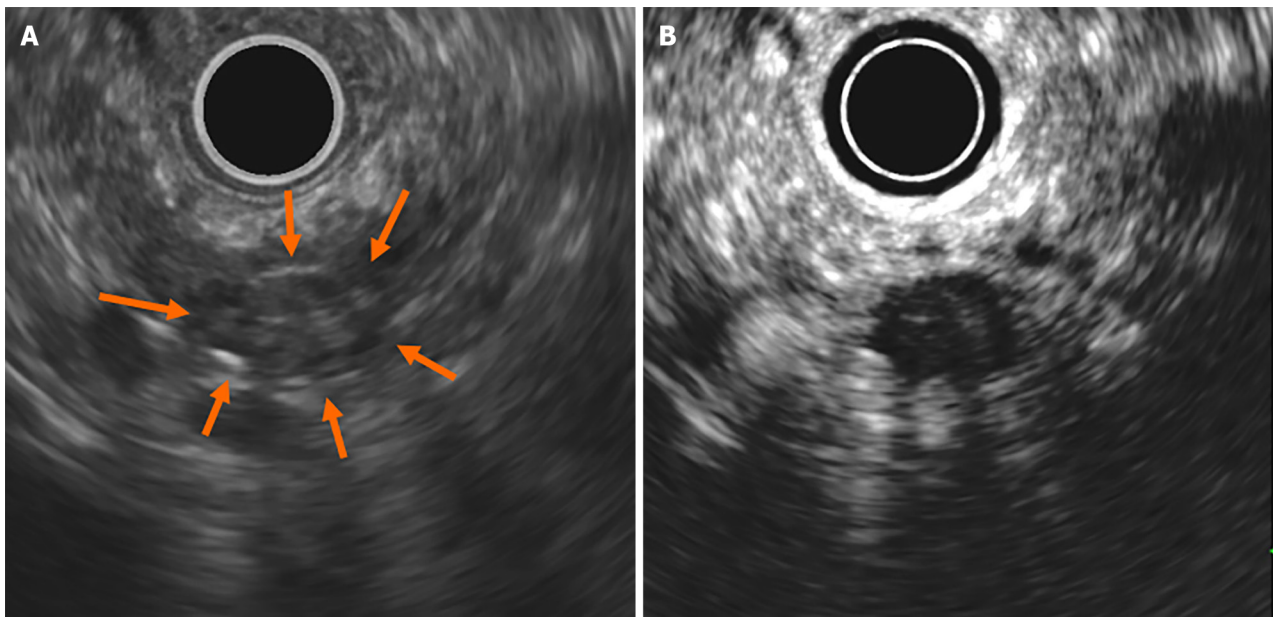


Figure 6 Findings of endoscopic ultrasonography at 24 months. A: On endoscopic ultrasonography (EUS), the cyst was described like a solid mass (arrows); B: Contrast-enhanced EUS using Sonazoid showed the mass as a round cyst.

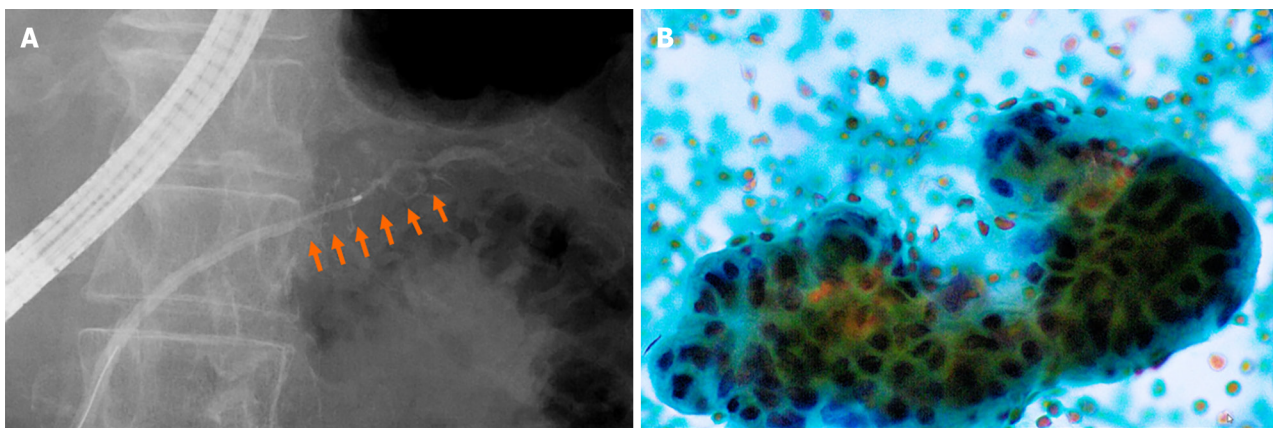


Figure 7 Findings of endoscopic retrograde pancreatography. A: Endoscopic retrograde pancreatography revealed that the main pancreatic duct (MPD) in the pancreatic tail was irregularly narrowing (arrows) in a 20-mm range and the caudal MPD was slightly dilated; B: Serial pancreatic juice aspiration cytology examination revealed atypical cells consistent with adenocarcinoma.

wall, causing a long and irregular MPD narrowing, which may have taken a long time for the caudal MPD dilation to become clear. Poor MPD visualization by MRCP, as in this case, is a finding that can be observed even in a normal pancreas. However, in this case, PanIN seems to have already existed two years ago. We believe that early diagnosis and treatment will be possible, considering that PanIN caused long and irregular strictures and cases with caudal cysts were numerous.

In this case, there was a challenge to our diagnostic strategy. Recently, fine needle aspiration using EUS (EUS-FNA) has been shown to improve diagnostic accuracy in pancreatic cystic neoplasm (PCN) when differentiating mucinous *vs* non-mucinous PCN, and malignant *vs* benign PCN, in cases where the diagnosis by CT or MRI is unclear[35]. We performed ERP, but not EUS-FNA, for the cyst due to concerns of needle tract seeding and peritoneal dissemination by aspiration for a pancreatic tail lesion. In Japan, aspiration for suspicion of cystic neoplasm is typically performed only as clinical research. As such, we need to pay attention to the development of a diagnostic strategy for PCN.

CONCLUSION

Here, we report a case of high-grade PanIN, which was diagnosed by continuous cytology of pancreatic juice based on changes in MRCP findings over time. This case was considered as very suggestive when considering an early diagnosis system for PC.

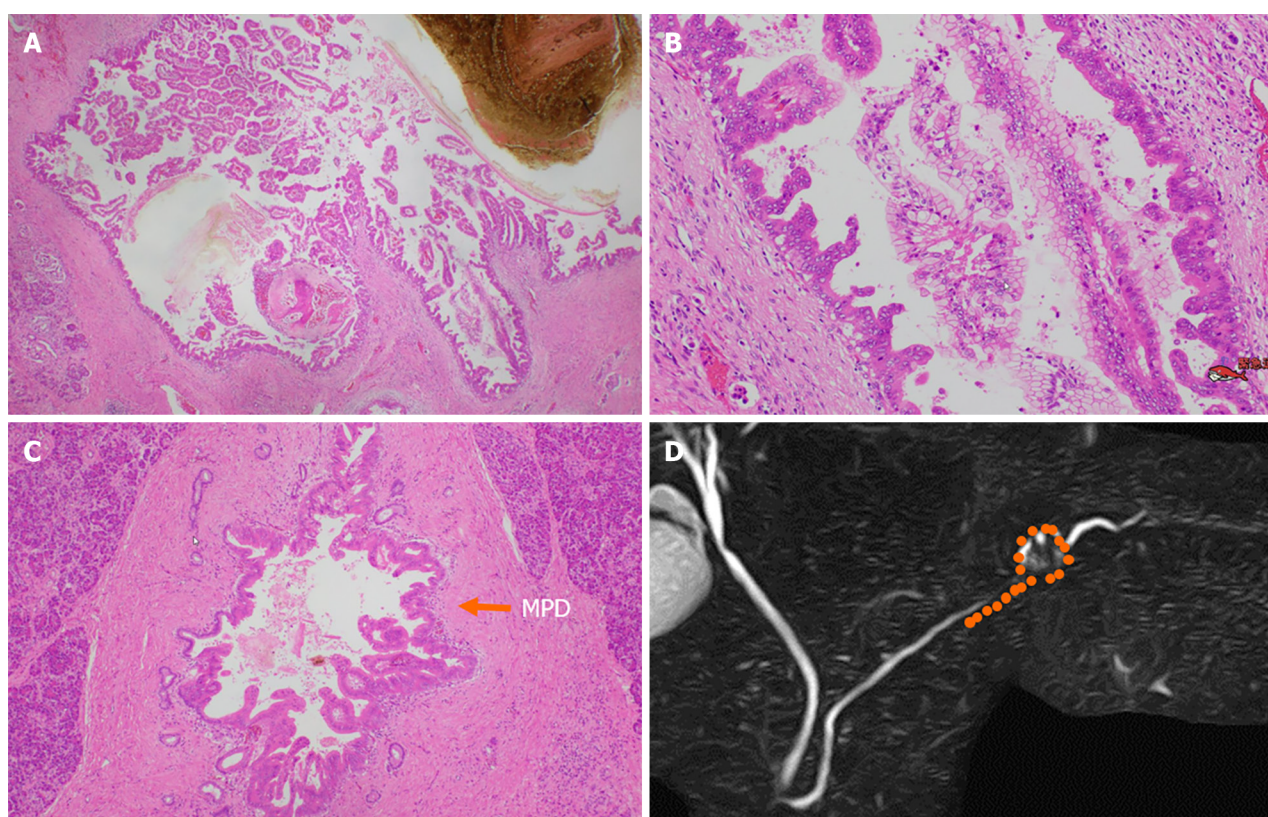


Figure 8 Pathological findings. A and B: Low-papillary and pseudopapillary adenocarcinoma cells were spread in the cyst wall; C: Malignant cells spread to the main pancreatic duct (arrow) and branch duct, in a 20-mm range toward the pancreatic body; D: Distribution of high-grade pancreatic intraepithelial neoplasia (orange points). MPD: Main pancreatic duct.

FOOTNOTES

Author contributions: Furuya N made substantial contributions to the study conception and design; Furuya N and Yamaguchi A were responsible for writing the original draft, and reviewing and editing the manuscript; Kato N, Sugata S, Hamada T, Shibata Y, and Tazuma S performed the data collection; Mizumoto T, Tamaru Y, Kusunoki R, Kuwai T, Kouno H, Sudo T, Kohno H, and Oka S revised the manuscript; Kuraoka K performed pathological diagnosis; all authors have read and approved the final manuscript.

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