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Case Report

Diagnosis of pancreatic intraepithelial neoplasia based on multimodal imaging findings: a case report and review of the literature

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Abstract: Pancreatic intraepithelial neoplasia (PanIN) is defined as a noninvasive epithelial neoplasm arising in the ductal epithelium and typically involving a duct of < 5 mm. PanIN is the most common precursor of conventional ductal adenocarcinoma of the pancreas. However, thus far, imaging findings for PanIN have not been clearly defined, complicating preoperative diagnosis. Herein, we report a case of pathologically proven PanIN with multimodal imaging findings. A 52-year-old female patient presented with a 1-month history of abdominal pain. Computed tomography (CT) and magnetic resonance (MR) imaging revealed multiple small, delayed enhancing nodules in the pancreas; these were described as hypoechoic, round-shaped nodules on endoscopic ultrasonography (EUS). Based on these image analyses, our differential diagnosis comprised a solid tumor of the pancreas, such as solid pseudopapillary neoplasm (SPN) or, with lower probability, pancreatic ductal adenocarcinomas (PDAC). However, the surgical pathologic result was determined to be PanIN-1B, with fibrosis and lobulocentric atrophy associated with chronic pancreatitis. Several reports, including our present case, have suggested that PanIN is accompanied by fibrosis, similar to that seen in chronic pancreatitis. We expect that awareness of this observation during imaging analysis may lead to earlier diagnosis of pancreatic cancer, and may therefore increase patient survival.

Keywords: Pancreatic neoplasms, precancerous conditions, multidetector computed tomography, magnetic resonance imaging, endosonography

Introduction

Pancreatic cancer is one of the most lethal malignancies, with a 5-year survival rate of < 8%; this rate has remained practically unchanged for decades [1]. A primary reason for this poor prognosis is that pancreatic cancer is often diagnosed late in the advanced stages of the disease; by that time, it is unresectable. This suggests that the early detection of pancreatic neoplasia is a critical factor that has the potential to improve the survival rate of patients with pancreatic cancer. Recently, it has been recognized that invasive pancreatic cancer arises from histologically noninvasive precursor lesions, including epithelial and cystic neoplastic lesions. Pancreatic intraepithelial neoplasia (PanIN) is the most common precursor of conventional ductal adenocarcinoma of the pancreas [2]. However, thus far, imaging findings for PanIN have not been clearly defined, complicating preoperative diagnosis [3, 4]. Herein, we report a case of pathologically proven PanIN with multimodal imaging findings.

Case presentation

A 52-year-old female patient presented with a 1-month history of abdominal pain. Physical examination of the patient was unremarkable, and she reported no notable medical history. Laboratory studies conducted at the time of admission showed that all v*alues* were within normal limits, *including amylase and lipase levels*. Levels of other tumor markers, such as carbohydrate antigen 19-9 (CA19-9), alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA), were also within normal ranges. An

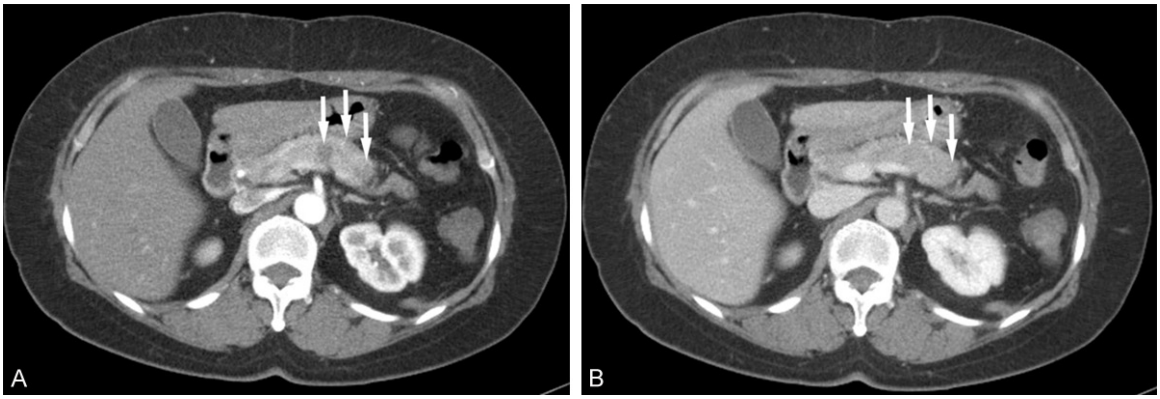

Figure 1. A 52-year-old female patient presented with pancreatic intraepithelial neoplasia 1-B. An abdominal computed tomography (CT) scan revealed ill-defined, small, low-density lesions (arrows, three of five lesions are shown in the image) in the pancreatic body and tail; these measured up to 14 mm on an arterial phase image (A). The lesions appeared isodense (arrows) on portal (B) and delayed phase images in CT scans and could not be distinguished from the pancreatic parenchyma.

abdominal computed tomography (CT) scan revealed ill-defined, small, low-density lesions in the pancreatic body and tail that measured up to 14 mm on an arterial phase image (**Figure 1A**). These five lesions appeared isodense on portal (**Figure 1B**) and delayed phase images in CT scans and could not be distinguished from the pancreatic parenchyma. The patient underwent magnetic resonance (MR) imaging (3.0-Tesla Intera Achieva; Philips Healthcare, Best, the Netherlands) for further examination. An axial unenhanced T1-weighted MR image (**Figure 2A**) also showed five hypointense lesions in the pancreatic body and tail, each measuring up to 15 mm, which showed mild enhancement on a gadoxetic acid-enhanced delayed phase MR image (**Figure 2B**). An axial respiratory-triggered single-shot T2-weighted MR image (**Figure 2C**) revealed five hyperintense and faintly visible duct-traversing pancreatic lesions, the so-called duct-penetrating sign. On an axial single-shot echo-planar diffusion weighted (DW) MR image (b = 800 s/mm^2) (**Figure 2D**) and an apparent diffusion coefficient (ADC) map (**Figure 2E**), five pancreatic lesions were detected with diffusion restriction. Endoscopic ultrasonography (EUS) (**Figure 3A**) revealed multiple hypoechoic, round-shaped nodules in the pancreatic body and tail. Fine needle aspiration of the solid pancreatic lesions was performed; cytology revealed only benign acinar and ductal cells and the absence of malignant cells. Fluorodeoxyglucose positron emission tomography (FDG PET/CT) (**Figure 3B**) showed no abnormal focal FDG uptake in pancreatic lesions.

These images revealed multifocal solid nodules in the pancreas, without definite obstruction of the main pancreatic duct. Nearby vascular invasion or distant metastasis was not noted. A diagnosis of solid pseudopapillary neoplasm (SPN) of the pancreas was initially considered. Although SPNs typically comprise a solitary mass and multicentricity is exceptionally rare, SPNs with multiple centers of origin have been sporadically reported in the literature [5]. In addition, there was no malignancy detected in cytology and the FDG PET/CT findings were negative; however, the possibility of malignant tumors, such as pancreatic ductal adenocarcinoma (PDAC), could not be ruled out. Therefore, distal pancreatectomy was performed. Grossly, the resected specimen from the pancreas appeared hardened with a creamy, white color; it lacked lobulation. No mass-like lesion was found within and no tumor cells were found upon frozen biopsy. Microscopic examination of the pancreatic lesion showed an epithelium consisting of mucin-producing columnar cells with basally located, round-to-oval, uniform nuclei with a papillary architecture, on a background of fibrosis and lobulocentric atrophy associated with chronic pancreatitis (**Figure 4**). The final diagnosis was reported as PanIN-1B (five lesions). The patient was in good condition at 12 months after the operation.

Discussion

PanINs are defined as noninvasive epithelial neoplasms arising in the ductal epithelium, typically involving ducts of < 5 mm. PanINs are

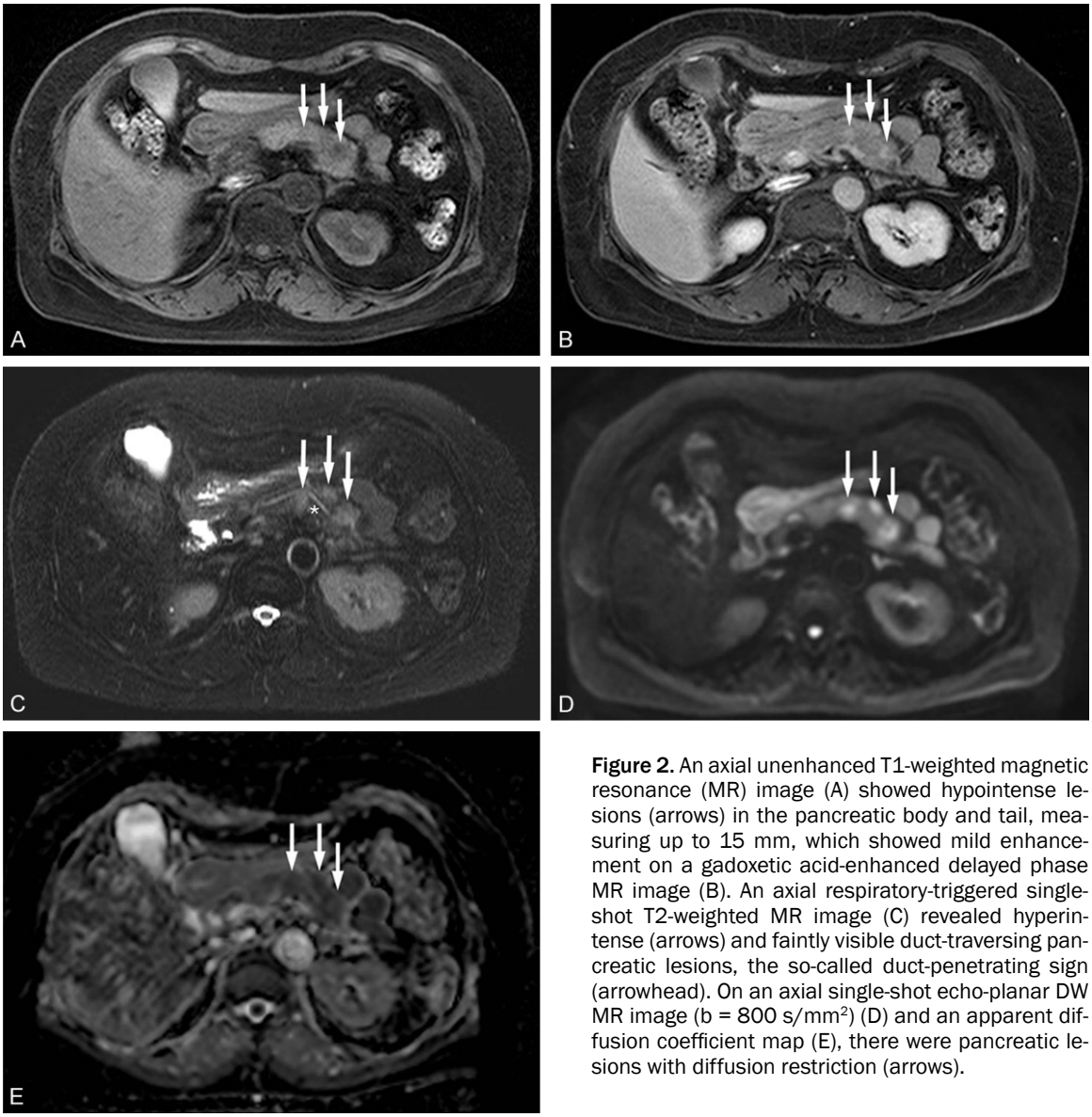

Figure 2. An axial unenhanced T1-weighted magnetic resonance (MR) image (A) showed hypointense lesions (arrows) in the pancreatic body and tail, measuring up to 15 mm, which showed mild enhancement on a gadoxetic acid-enhanced delayed phase MR image (B). An axial respiratory-triggered single-shot T2-weighted MR image (C) revealed hyperintense (arrows) and faintly visible duct-traversing pancreatic lesions, the so-called duct-penetrating sign (arrowhead). On an axial single-shot echo-planar DW MR image (b = 800 s/mm^2) (D) and an apparent diffusion coefficient map (E), there were pancreatic lesions with diffusion restriction (arrows).

microscopic, papillary, or flat, and are characterized by columnar to cuboidal cells with varying amounts of mucin. They are classified histologically as PanIN-1 (low-grade; subdivided into PanIN-1A (flat) and PanIN-1B (papillary)), PanIN-2 (intermediate-grade), or PanIN-3 (high-grade), based on the degree of cytologic and architectural atypia present in the lesion [6]. PanIN is not the only precursor of invasive pancreatic cancer: intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, for example, also represent preinvasive stages of carcinoma, but PanIN is the most common and important precursor of conventional ductal adenocarcinomas of the pancreas [6].

PanIN is often surrounded by lobular parenchymal atrophy [7-9]. PanIN lesions are suspected to block exocrine outflow of the ducts, resulting in the secretion of acinar enzymes and leading to substantial autodigestion of the parenchyma; this causes pancreatitis-like atrophy. Therefore, it seems that PanIN does not occur because of atrophy; conversely, PanIN may occur first, causing obstruction of small ducts that progresses to multifocal lobulocentric atrophy [8]. PanINs are also commonly found when evaluating cystic lesions in the pancreas. Regarding the cystic lesions associated with PanIN, atrophy and fibrosis of acinar tissue is suspected to cause inflammation around, and

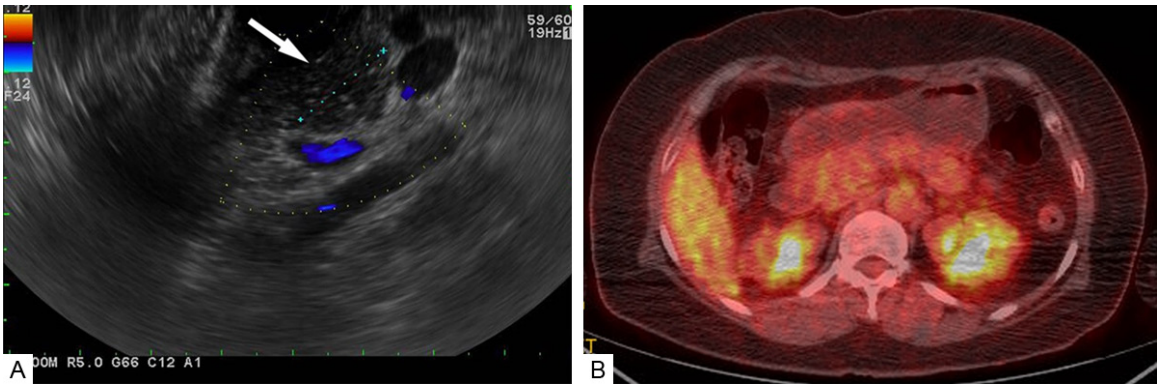

Figure 3. Endoscopic ultrasonography (EUS) (A) revealed multiple hypoechoic, round-shaped nodules (arrow) in the pancreatic body and tail. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) (B) showed no abnormal focal FDG uptake in the pancreatic lesions.

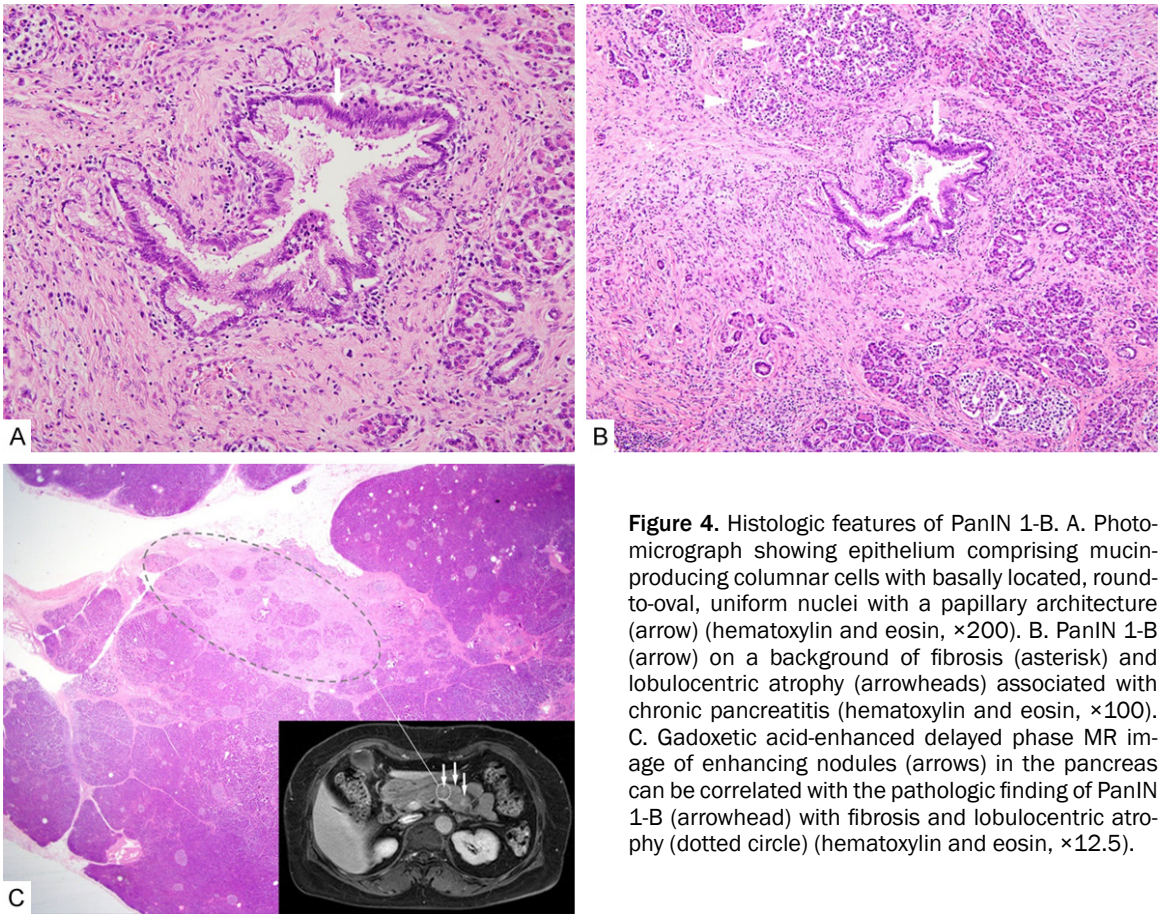

Figure 4. Histologic features of PanIN 1-B. A. Photomicrograph showing epithelium comprising mucin-producing columnar cells with basally located, round-to-oval, uniform nuclei with a papillary architecture (arrow) (hematoxylin and eosin, ×200). B. PanIN 1-B (arrow) on a background of fibrosis (asterisk) and lobulocentric atrophy (arrowheads) associated with chronic pancreatitis (hematoxylin and eosin, ×100). C. Gadoxetic acid-enhanced delayed phase MR image of enhancing nodules (arrows) in the pancreas can be correlated with the pathologic finding of PanIN 1-B (arrowhead) with fibrosis and lobulocentric atrophy (dotted circle) (hematoxylin and eosin, ×12.5).

stenosis of, the pancreatic duct; this results in dilation of the main pancreatic duct and the formation of cystic lesions in the tail of the pancreas [10].

PanINs are defined as intraepithelial lesions; notably, image-based evaluation provides little direct evidence for their detection. However, their presence can be indirectly inferred from imaging studies, and there have been a few reports of imaging findings of PanINs (**Table 1**). Each PanIN produces a small fibrous area known as lobulocentric atrophy; when multiple PanIN lesions are present, these fibrotic areas

Table 1. Summary of clinical characteristics and radiologic features of previously reported cases of PanIN

Reference	Age	Sex	Symptom	Location in pancreas	Finding on CT	Finding on MRI	Finding on ERCP	Finding on EUS	Treatment	Pathology	Follow up
Sohn et al., 2008 [11]	49	F	Epigastric pain	Body	Focal enhancement of the pancreatic body with obliteration of the pancreatic duct	NA	Segmental narrowing of the pancreatic duct	Small, well-demarcated lower echoic round mass	Distal pancreatectomy	PanIN-3 with tumor-forming chronic pancreatitis	NED
Lee et al., 2010 [12]	72	M	Abdominal pain	Body	Neither abnormal mass-like lesion nor pancreatic ductal dilation is observed	NA	Stricture of the pancreatic duct in the pancreatic body without dilation of the upstream pancreatic duct (tail)	NA	Subtotal pancreatectomy	PanIN-3 with chronic pancreatitis	NED
Algin et al., 2011 [13]	58	M	Right upper quadrant pain	Head	Small, low-density nodule	Pancreatic cystic lesion with enhanced thin septa and wall	NA	NA	Excision	PanIN-3	NED at 6 months
Ito et al., 2015 [14]	63	F	Epigastric pain	Body	Cystic lesion with relatively thick septum-like structure and a solid component with contrast enhancement inside the cyst	Multilocular cystic lesion and continuity with the main pancreatic duct that was slightly dilated more distally	No abnormalities in the papillae or an irregular stricture of the main pancreatic duct	Multilocular cystic lesion communicating with dilated main pancreatic duct and extensive node-like raised lesions with papillary development from the cyst to the main pancreatic duct	Total pancreatectomy	PanIN-2 to PanIN-3	NED at 5 years
Present case	52	F	Abdominal pain	Body and tail	Ill-defined, small, low-density lesions on an arterial phase image and isodense on portal and delayed phase images	Hyperintense lesions with faintly visible duct-traversing pancreatic lesions, the so-called duct-penetrating sign on T2-weighted image and mild enhancement on delayed phase image with diffusion restriction	NA	Multiple hypoechoic, round-shaped nodules	Distal pancreatectomy	PanIN-1B	NED at 12 months

Note: PanIN, pancreatic intraepithelial neoplasia; F, female; M, male; NED, no evidence of disease; NA, data not available.

can appear to be features of chronic pancreatitis. Chronic pancreatitis-like changes that have been reported in EUS and endoscopic retrograde cholangiopancreatography (ERCP) observations include abnormalities of the pancreatic ducts (ectasia, irregularity, and saccules) and the parenchyma (heterogeneity and lobularity) [4, 7, 11, 12]. There are also reports of ductal stenosis and distal cystic lesions around PanIN, resulting from the atrophy and fibrosis of pancreatic tissue, which have been noted in both CT and MR examinations [13, 14] (**Table 1**).

In the present case, CT and MR imaging revealed multiple small, delayed enhancing nodules in the pancreas, which were reported as hypoechoic, round-shaped nodules on EUS. The nodules exhibited the duct-penetrating sign without obstruction of the main pancreatic duct. Based on these image analyses, our differential diagnosis comprised a solid tumor of the pancreas, such as SPN, or, with lower probability, PDAC. However, the surgical pathologic result was determined to be PanIN-1B, with fibrosis and lobulocentric atrophy associated with chronic pancreatitis. In retrospect, our findings of delayed enhancing nodules in the pancreas can be interpreted as forms of inflammation characterized by an abundance of fibrotic tissue, not infrequently seen in mass-forming chronic pancreatitis [15, 16]. The duct-penetrating sign seen in our case is consistent with a previous report that suggests that the lesion supports the inflammatory pancreatic mass, rather than the tumorous lesion [17]. The diffusion restriction of the nodules seen on MR images in our case can also be explained in a context similar to the findings associated with chronic inflammatory processes in mass-forming pancreatitis and autoimmune pancreatitis, due to increased cellularity from the dense infiltration of lymphocytes and plasma cells [16]. In our case, neither the imaging findings nor the pathologic results showed evidence of ductal stenosis or distal cystic lesions that have been reported in previous cases [13, 14]. This may be the result of differences in histological grades in each case.

Recent insight into the development of pancreatic carcinogenesis postulates a stepwise progression from low-grade to high-grade PanIN and then to invasive cancer [18, 19]. Molecular studies are also underway, which involve the use of genomic modifications as biomarkers in multistep tumor progression models in order to detect and differentiate among precursor lesions of pancreatic cancer [20].

Although it is extremely difficult to diagnose PanIN before surgery, careful attention and persistent observation of secondary changes related to microscopic lesions, with multiple modalities, can make detection possible. There are a few reports regarding the imaging findings of PanIN-3; however, to our knowledge, there are no reports regarding multimodal imaging of PanIN-1 in the literature. Few cases have been reported thus far; therefore, we need to organize and review more cases in the future. The observed changes could be used as a screening test for the presence of PanIN in pancreatic cancer at-risk groups. Early detection of premalignant lesions may reduce morbidity by preventing invasive and extensive surgical procedures, and may consequently increase the survival of patients with pancreatic cancer.

In conclusion, we have presented a case of pathologically proven PanIN with multimodal imaging findings. PanIN lesions are the most common precursors of conventional ductal adenocarcinomas of the pancreas; however, image-based evaluation provides little direct evidence of their existence. Several reports thus far, including our present case, suggest that PanIN is accompanied by fibrosis, similar to that observed in chronic pancreatitis. We expect that awareness of this observation during imaging analysis will lead to earlier diagnosis of pancreatic cancer, and may therefore increase patient survival.

Disclosure of conflict of interest

None.

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