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 values 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
PanIN based on multimodal imaging findings

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/mm²) (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...
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
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

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

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

can appear to be features of chronic pancreati-
tis. Chronic pancreatitis-like changes that have 
been reported in EUS and endoscopic retro-
grade cholangiopancreatography (ERCP) obser-
vations 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 pan-
creatic 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 dif-
ferential diagnosis comprised a solid tumor of 
the pancreas, such as SPN, or, with lower prob-
ability, 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 inflam-
mation 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-form-
ing chronic pancreatitis and autoimmune pancreatitis, 
due to increased cellularity from the dense infil-
tration 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 pancre-
atic carcinogenesis postulates a stepwise pro-
gression 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 orga-
nize 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 premal-
gnant lesions may reduce morbidity by pre-
venting invasive and extensive surgical proce-
dures, and may consequently increase the sur-

evival 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 
adeno-carcinomas 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 
extpect that awareness of this observation dur-
ing imaging analysis will lead to earlier diagno-
sis of pancreatic cancer, and may therefore 
increase patient survival.

Disclosure of conflict of interest

None.

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