Case Reports in Oncology

Case Rep Oncol 2015;8:30–36

DOI: 10.1159/000371842
Published online: January 22, 2015

1662–6575/15/0081–0030$39.50/0
www.karger.com/cro

A Case of Pancreatic Intraepithelial Neoplasia That Was Difficult to Diagnose Preoperatively

Hiroyuki Ito[a] Yoshiaki Kawaguchi[a] Yohei Kawashima[a]
Atsuko Maruno[a] Masami Ogawa[a] Kenichi Hirabayashi[b]
Tetsuya Mine[a]

Departments of [a]Gastroenterology and [b]Pathology, Tokai University School of Medicine, Isehara, Japan

Key Words
Pancreatic intraepithelial neoplasia · Pancreas cancer · Pancreatic duct stenosis · Pancreatic cyst · Diagnosis

Abstract
A 63-year-old female patient presented to a local physician with pain in her back and epigastric region. An abdominal computed tomography (CT) scan revealed a pancreatic tumor, and the patient was referred to our hospital. Multiple imaging studies that included ultrasonography (US), CT, MRI, and endoscopic US revealed a cystic lesion 3–4 cm in size with node-like projections in the body of the pancreas. The distal main pancreatic duct was also found to be dilated. Endoscopic retrograde pancreatography revealed an irregular stenosis of the main pancreatic duct proximal to the cystic lesion, and malignancy was suspected. The patient was preoperatively diagnosed with pancreatic ductal carcinoma concomitant with intraductal papillary mucinous carcinoma, and a distal pancreatectomy was performed. Rapid pathological diagnosis during surgery revealed positive surgical margins for pancreatic intraepithelial neoplasia (PanIN). Further resection was performed twice, her surgical margin was positive and total pancreatectomy was ultimately conducted. Histopathological findings revealed diffuse microinvasive cancerous lesions corresponding to PanIN-2 (moderate dysplasia) to PanIN-3 (carcinoma in situ) throughout the pancreas. PanIN involves microlesions of the ductal epithelium that may precede pancreatic cancer. Ascertaining changes in PanIN using images provided by diagnostic modalities such as CT and US is challenging. Ductal stenosis and distal cystic lesions resulting from atrophy and fibrosis of pancreatic tissue were noted around PanIN. Considering the possibility of PanIN, a precancerous lesion during differential

Yoshiaki Kawaguchi, MD, PhD
Department of Gastroenterology
Tokai University School of Medicine
143 Shimokasuya, Isehara, 259-1193 (Japan)
E-Mail y711kawa@is.icc.u-tokai.ac.jp

diagnosis will help to improve early detection and prognosis for patients with pancreatic cancer.

Introduction

Pancreatic cancer is known to have the poorest prognosis of all cancers. This is due to the anatomical location of the pancreas, the speed of tumor invasion and development, and the difficulty of early detection. Thus, identifying patients with a high risk of pancreatic cancer and screening them carefully is important for overcoming the disease. However, identification of high-risk patients is difficult. In recent years, the concept of pancreatic intraepithelial neoplasia (PanIN) as a lesion preceding pancreatic cancer has become clearer, and the interest for PanIN has increased as a potential method for the early detection of pancreatic cancer. The current case described herein was difficult to diagnose: both intraductal papillary-mucinous carcinoma (IPMC) and pancreatic ductal carcinoma were suspected, and a resection was performed. However, the lesions turned out to be primarily PanIN. Herein we describe how this case provides valuable guidance for future diagnoses.

Case Report

The patient was a 63-year-old woman who was seen by a local physician for pain in the epigastric region that started back in December 2006. An abdominal CT scan revealed pancreatic cystic lesions and pancreatic duct dilatation, and the patient was referred to our hospital for further examination on December 27. The patient had a history of hyperlipidemia for which she was being treated, but no history of pancreatitis or abdominal trauma, and no notable family history. The patient did not smoke or drink alcohol. Examination results on admission were as follows: height, 157 cm, weight, 40 kg, and body temperature 37.2°C. The patient was alert and her abdomen was soft and flat with no palpable masses. The patient had tenderness in the epigastrium but no rebound or guarding.

Her blood chemistry revealed a slight elevation of the pancreatic enzymes amylase and elastase 1. While no other evidence of inflammation could suggest active pancreatitis, a slight elevation of the tumor marker CA19-9 was detected.

Abdominal ultrasonography (US) revealed a multilocular cystic lesion of 45 mm in length with node-like projections in the body of the pancreas. The main pancreatic duct was noticeably dilated from the body to the tail. The pancreatic parenchyma was overall atrophic, and her echogenicity was moderate. Comorbidity with chronic pancreatitis was suspected. An abdominal CT revealed a cystic lesion with a relatively thick septum-like structure in the body of the pancreas. A solid component with slight contrast enhancement was noted inside the cyst. Magnetic resonance cholangiopancreatography revealed a multilocular cystic lesion in the body of the pancreas, and continuity with the main pancreatic duct that was slightly dilated more distally was suspected (fig. 1). Endoscopic US revealed a multilocular cystic lesion (26 mm long) in the body of the pancreas. A dilated main pancreatic duct communicating with this lesion was noted. There were extensive node-like raised lesions with papillary development from the cyst to the main pancreatic duct. Like the findings of US, the pancreatic parenchyma was atrophic and echogenicity was moderate, again alluding to comorbidity with chronic pancreatitis. Masses other than the cyst were not seen in the pancreatic parenchyma, which included the area around the main pancreatic duct proximal to the cyst. Endoscopic retrograde pancreatography (ERP) did not reveal marked

abnormalities in the papillae or an irregular stricture of the main pancreatic duct in the area between the pancreatic head and body. The distal portion of the pancreatic duct was dilated (fig. 2). An ERP catheter and catheter for brush cytology were unable to pass the stricture. Pancreatic juice cytology was class I, and malignancy was not detected.

These images revealed a multilocular cystic lesion with internal nodes and A dilatation of the main pancreatic duct. A diagnosis of a combined type IPMC was first considered. Though cytology revealed no malignancy, and examinations such as endoscopic US failed to detect obvious masses, ERP revealed an irregular ductal stricture in the portion of the pancreas head proximal to a cystic lesion. Therefore, comorbidity with small pancreatic ductal carcinoma was suspected. Nearby vascular invasions or distant metastasis were not noted. Distal pancreatectomy was then performed in February 2007.

Surgical findings were as follows: the pancreas was hard throughout, and a multilocular cystic lesion of 4 cm in length was noted in the body of the pancreas. At the site where an irregular ductal stricture proximal to the cystic lesion was noted preoperatively, the pancreatic tissue was hard and mass like, so resection was performed more proximally. A rapid pathological diagnosis of the surgical margin during surgery revealed evidence of PanIN, and further resection was performed twice. The surgical margin was positive, and so total pancreatectomy was ultimately conducted.

Histopathological findings were as follows: diffuse lesions corresponding to PanIN-2 to PanIN-3 [carcinoma in situ (CIS)] were noted primarily in the main pancreatic duct (fig. 3a). Multiple intraepithelial papillary lesions were noted in a multilocular cystic lesion and the dilated main pancreatic duct (fig. 3b). The irregular stricture of the pancreatic duct in the head of the pancreas was severely fibrotic, and papillary growth of intraepithelial lesions (corresponding to PanIN-2 and CIS) was noted (fig. 3c). In addition, numerous small pseudocysts were found around the stricture. Immunostaining indicated a positivity for MUC5AC and MUC6, partial positivity for MUC2, and negativity for MUC1.

Postoperatively, the patient developed secondary diabetes mellitus and required insulin treatment. The patient also required high doses of pancreatic enzyme supplements but did not experience tumor recurrence after being followed up for approximately 5 years.

Discussion

PanIN as a precursor of pancreatic cancer is a concept put out by Hruban et al. [3] in 2000. PanINs are defined as microscopic papillary or flat, noninvasive epithelial neoplasms arising in the ductal epithelium. PanINs are characterized by columnar to cuboidal cells with varying amounts of mucin and different degrees of cytological and architectural atypia, and they usually involve ducts of less than 5 mm [1, 2]. PanINs are categorized into 3 grades, PanIN-1 to PanIN-3, depending on the extent of histological atypia. PanIN-1 is further divided into PanIN-1A (mucinous hypertrophy or nonpapillary hyperplasia) and PanIN-1B (papillary hyperplasia). PanIN-3 corresponds to CIS and is the PanIN grade with the most significant atypia; this grade is frequently associated with genetic abnormalities [4].

PanINs are intraepithelial lesions, and there is little image-based evidence of their existence before a pancreatic resection. These lesions are extremely rare, even when considering diagnosed cases of atypical hyperplastic lesions of the pancreas and CIS, and account for 0.13% of all cases of pancreatic cancer in the pancreatic cancer registry of the Japan Pancreas Society in 2003 [5]. However, Kozuka et al. [6] studied autopsies in 1,174 deaths due to other causes in 1979 and found nonpapillary hyperplasia corresponding to PanIN-1A in the pancreas of 33% of individuals aged 60 and over. Similarly, they reported finding papillary

hyperplasia corresponding to PanIN-1B in 13% of individuals. It thus appears that a considerable number of people have PanINs. The same study indicated that lesions corresponding to PanIN-1 were found beginning in the late teens with incidences increasing with age and more likely to occur in men. Atypical hyperplasia corresponding to PanIN-3 was rarely found in younger individuals, but it was found in 3% of those aged 60 and over. Lesions were almost twice as likely to be found in the head of the pancreas than in the tail.

PanINs are defined as lesions only found in the epithelium, so obtaining direct evidence of a mass by CT or US is difficult. PanINs are often detected when evaluating cystic lesions in the pancreas. Of 22 PanIN cases reported in Japan, 6 were identified when a cystic lesion was examined more closely [7]. Regarding the mechanism of PanIN cyst formation, Nakaizumi et al. [8] reported that atrophy and fibrosis of acinar tissue due to PanIN causes inflammation around the pancreatic ducts, resulting in stenosis and dilatation of the main pancreatic duct and multiple cystic lesions towards the tail. Existence of a multilocular cystic lesion in the current case was assumed to have been caused by a similar mechanism. In addition, the current patient was initially seen for epigastric and back pains and was suspected of having developed pancreatitis due to a ductal stricture and impaired outflow of pancreatic juice.

The pathological characteristics of PanINs are similar to those of intraductal papillary mucinous neoplasms (IPMNs), which involve lesions preceding pancreatic ductal carcinoma. An IPMN, however, will have dilated pancreatic ducts due to excessive mucin production or prominent papillary growth. A PanIN, in contrast, has a flat or serrated papillary structure, and pancreatic duct dilatation will mostly be secondary, having resulted from an inflammatory stricture [9]. A ductal stricture and cyst were noted in the current case. CIS and epithelial papillary growths are more often noted in tissue surrounding a ductal stricture than in other sites. The ductal stricture is presumed to occur via a mechanism similar to typical pancreatic ductal carcinoma. There is also severe inflammation around the cysts. Stricture due to inflammation of pancreatic ductules results in numerous cysts; such cysts were recognized as multilocular cystic lesions in the current case.

Patients who are considered to be at high risk of PanIN include: (1) patients, where pancreatic cysts, pancreatic duct dilatations or pancreatic masses by diagnostic imaging, such as abdominal US and CT or MRI, were found, (2) patients with diabetes, (3) patients with a history of chronic pancreatitis or acute pancreatitis, and (4) patients with IPMN [7]. Periodic follow-up with various imaging techniques is recommended in these cases. When abnormalities are detected in images, a more detailed examination in the form of ERP or cytology is needed.

With regard to prognosis, patients diagnosed with PanIN postoperatively are reported to have a wide-ranging survival time from 1 year and 5 months to 29 years [10]. Given that PanIN-3 takes many years to develop into a malignancy, PanIN has a better prognosis than the more common invasive cancer. Depending on the patient, local treatment involving a partial pancreatectomy may prevent recurrence, and detection in early stages allows for the choice of minimally invasive surgery.

The current case was difficult to diagnose as PanIN preoperatively. On images, PanIN appears as varying degrees of stricture in the main pancreatic duct or pancreatic ductules, indicating intraepithelial fibrosis. PanIN is also evident as multiple small cystic lesions of different sizes. Awareness of these details and recognizing even minor changes in images are crucial to the early detection of pancreatic cancer.

References

1 Hruban RH, Goggins M, Parsons J, et al: Progression model for pancreatic cancer. Clin Cancer Res 2000;6:2969–2972.
2 Hruban RH, Takaori K, Klimstra DS, et al: An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 2004;28:977–987.
3 Hruban RH, Adsay NV, Aldores-Saavedra J, et al: Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol 2001;25:579–586.
4 Furukawa T, Chiba R, Kobari M, et al: Varying grades of epithelial atypia in the pancreatic ducts of humans. Classification based on morphometry and multivariate analysis and correlated with positive reactions of carcinoembryonic antigen. Arch Pathol Lab Med 1994;118:227–234.
5 Japan Pancreatic Society Registration Board of Pancreatic Cancer. Suizo 2003;18:101–169.
6 Kozuka S, Sassa R, Taki T, et al: Relation of pancreatic hyperplasia to carcinoma. Cancer 1979;43:1418–1428.
7 Yano K, Chijiiwa K, Ouchida J, et al: A Resected case of carcinoma in situ (PanIN-3) initially suggested by the cystic lesion – report of a case and review of the literature. Tan To Sui 2006;27:583–587.
8 Nakaizumi A, Tanaka Y, Oshikawa O, et al: Synchronous and metachronous occurrence of branch type IPMT and invasive ductal carcinoma of the pancreas. Tan To Sui 2002;23:1013–1019.
9 Takaori K, Kobashi Y, Matsusue S, et al: Clinicopathological features of pancreatic intraepithelial neoplasias and their relationship to intraductal papillary-mucinous tumors. J Hepatobiliary Pancreat Surg 2003;10:125–136.
10 Takaori K, Matsusue S, Fujisawa T, et al: Carcinoma in situ of the pancreas associated with localized fibrosis: a clue to early detection of neoplastic lesions arising from pancreatic ducts. Pancreas 1998;17:102–105.

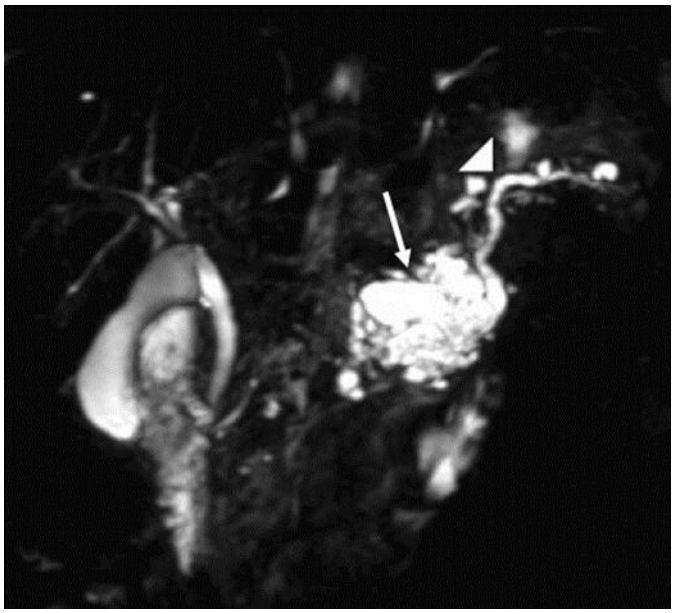

Fig. 1. Magnetic resonance cholangiopancreatography revealed a multilocular cystic lesion in the body of the pancreas (arrow) and continuity with the main pancreatic duct that was slightly dilated more distally was suspected (arrowhead).

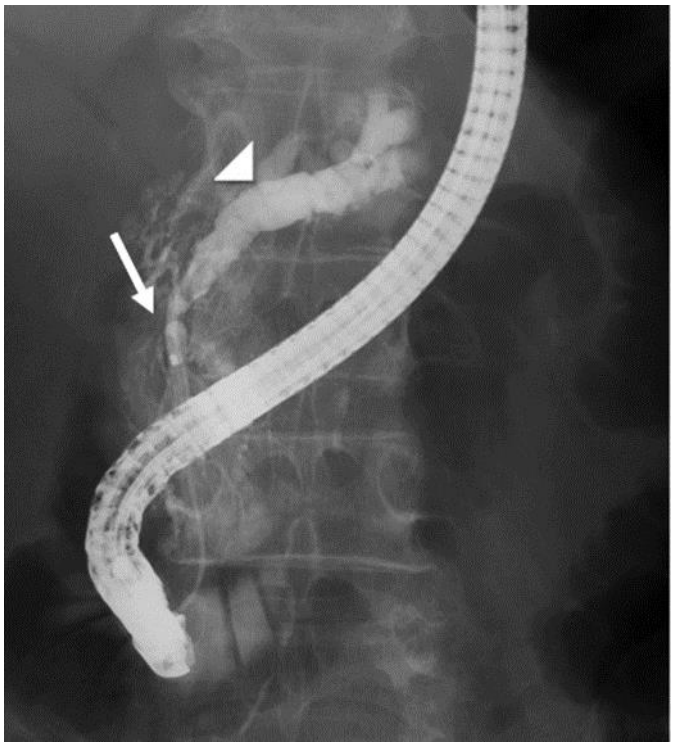

Fig. 2. ERP revealed irregular stricture of the main pancreatic duct in the area between the pancreatic head and body (arrow). The distal portion of the pancreatic duct was dilated (arrowhead).

Case Rep Oncol 2015;8:30–36
DOI: 10.1159/000371842

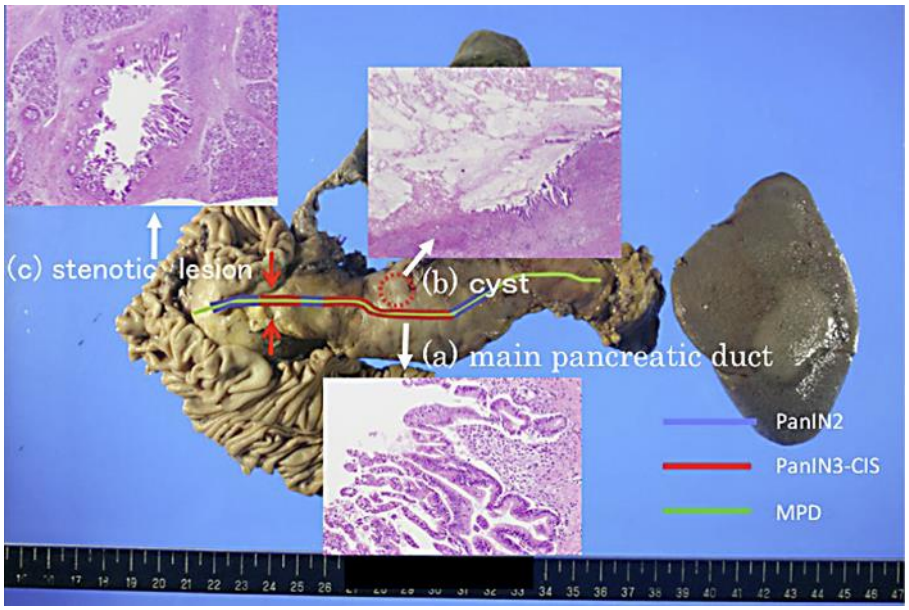

Fig. 3. Histopathological findings. Diffuse lesions corresponding to PanIN-2 to PanIN-3 (carcinoma in situ) were noted primarily in the main pancreatic duct (a). Multiple intraepithelial papillary lesions were noted in a multilocular cystic lesion (b). The irregular stricture of the pancreatic duct in the head of the pancreas was severely fibrotic, and papillary growth of intraepithelial lesions (corresponding to PanIN-2 and carcinoma in situ) was noted (c).