Case Reports in Oncology

Case Rep Oncol 2017;10:143–150

DOI: 10.1159/000456611
Published online: February 2, 2017

Case Report

A Serous Cystic Neoplasm of the Pancreas Coexisting with High-Grade Pancreatic Intraepithelial Neoplasia Mimicking an Intraepithelial Papillary Mucinous Neoplasm: A Case Report

Aya Kawanishi[a] Kenichi Hirabayashi[b] Hirotaka Kono[b] Yumi Takanashi[b] Atsuko Hadano[a] Yohei Kawashima[a] Masami Ogawa[a] Yoshiaki Kawaguchi[a] Misuzu Yamada[c] Toshio Nakagohri[c] Naoya Nakamura[b] Tetsuya Mine[a]

[a]Department of Gastroenterology and Hepatology, Tokai University School of Medicine, Isehara, Japan; [b]Department of Pathology, Tokai University School of Medicine, Isehara, Japan; [c]Department of Surgery, Tokai University School of Medicine, Isehara, Japan

Keywords
Neoplasms · Serous and cystic neoplasms · Pancreas · VHL protein · Intraepithelial

Abstract
Serous cystic neoplasms of the pancreas are rare exocrine pancreatic neoplasms, most of which are benign and do not communicate with the pancreatic duct. Pancreatic intraepithelial neoplasm (PanIN) is considered a precursor of ductal adenocarcinoma that is microscopically recognized in pancreatic ducts. A 67-year-old Japanese woman presented with a 10-mm multilocular cystic lesion at the pancreatic body. Magnetic resonance pancreatography showed stenosis of the main pancreatic duct at the pancreatic body and dilatation of the distal side of the main pancreatic duct. Furthermore, communication between the cystic lesion and the main pancreatic duct was suspected based on magnetic resonance pancreatography findings. Distal pancreatectomy was performed under the preoperative diagnosis of intraductal papillary mucinous neoplasm. Histologically, the cystic lesion was lined with a

KARGER

Kenichi Hirabayashi, MD, PhD
Department of Pathology
Tokai University School of Medicine
143 Shimokasuya, Isehara, Kanagawa 259-1193 (Japan)
E-Mail kenichi.hirabayashi@tokai.ac.jp

non-atypical cuboidal or flat epithelium with clear cytoplasm and was thus diagnosed as a serous cystic neoplasm. High-grade PanIN lesions with stromal fibrosis were observed at the main and branch pancreatic ducts. Histological examination revealed no communication between the serous cystic neoplasm and the pancreatic ducts. Immunohistochemically, the epithelium of the serous cystic neoplasm showed positive anti-von Hippel-Lindau antibody staining, whereas the epithelium of the PanIN showed negative staining. A serous cystic neoplasm coexisting with another pancreatic neoplasm is rare. When dilatation of the main or branch pancreatic ducts coexists with a serous cystic neoplasm, as in this case, the lesion clinically mimics an intraductal papillary mucinous neoplasm.

Introduction

Serous cystic neoplasms (SCNs) of the pancreas are rare exocrine pancreatic neoplasms, most of which are benign [1] and usually do not communicate with the pancreatic duct [1]. A pancreatic intraepithelial neoplasm (PanIN) is considered to be a precursor of ductal adenocarcinoma that is usually <5 mm in size and is microscopically recognized in pancreatic ducts [2]. In contrast, an intraductal papillary mucinous neoplasm (IPMN) is a grossly visible, mucin-producing, predominantly papillary epithelial neoplasm arising from the main pancreatic duct or branch ducts, with varying degrees of ductal dilatation. An IPMN is usually >1 cm in diameter and includes a variety of cell types with a wide spectrum of cytological and architectural atypias [2]. In this report, we present an extremely rare case of a pancreatic SCN coexisting with a high-grade PanIN, mimicking an IPMN.

Case Report

A 67-year-old Japanese woman was admitted to our hospital because of a multilocular cystic lesion measuring 10 mm at the pancreatic body, which had been detected by abdominal ultrasonography during a routine medical examination. She had no significant medical history and no significant family history, including of von Hippel-Lindau (VHL) disease. She did not smoke or drink alcohol. She had no symptoms, and physical examination revealed no abnormal findings.

Abdominal contrast-enhanced computed tomography revealed a multilocular cystic lesion measuring 10 mm at the pancreatic body, the wall of which had no solid component, enhanced with contrast media. Magnetic resonance pancreatography (MRP) showed stenosis of the main pancreatic duct at the pancreatic body and dilatation of the distal side of the main pancreatic duct (Fig. 1a). Furthermore, communication between the cystic lesion and the main pancreatic duct was suspected based on the MRP findings. Endoscopic retrograde pancreatography (ERP) showed stenosis of the main pancreatic duct at the pancreatic body and dilatation of the distal side of the main or branch pancreatic ducts (Fig. 1b). The stenosis of the main pancreatic duct was distant from the cystic lesion. ERP could not prove a communication between the main pancreatic duct and the cystic lesion. Endoscopic ultrasonography showed a multilocular cystic lesion with septal structures at the pancreatic body, whereas an intramural nodule or mass shadow was not found (Fig. 1c). Consequently, distal pancreatectomy was performed under the preoperative diagnosis of IPMN with invasion.

Macroscopically, there were multiple cystic lesions measuring 10 mm in diameter in the pancreatic body. Histologically, the cystic lesions were lined with a cuboidal or flat epithelium with small round nuclei and clear cytoplasm. The cystic lesion was diagnosed as an SCN. The stenotic main pancreatic duct and branch ducts around the stenotic main pancreatic duct were lined by a low-papillary epithelium with enlarged nuclei and nuclear pseudostratification. There was no invasion. These lesions were diagnosed as high-grade PanIN (PanIN-2 or -3) (Fig. 2). Stromal fibrosis was observed around the high-grade PanIN lesions. Immunohistochemically, the epithelium of the SCN was positive for the anti-VHL antibody (polyclonal; dilution 1:200; Santa Cruz Biotechnology, Santa Cruz, CA, USA), whereas the epithelium of the PanIN was negative for it (Fig. 3). Communication between the SCN and the main pancreatic ducts was not identified in the resected specimen. The final pathological diagnosis was SCN combined with high-grade PanIN of the main and branch pancreatic ducts.

Discussion

SCN usually has a sponge-like appearance, comprising multiple micro- or oligocysts lined by flattened or cuboidal glycogen-rich cells. Nuclear atypia and malignant changes are very rare in SCN [3].

PanIN is a microscopic, non-invasive epithelial neoplasm arising in the pancreatic ducts; it usually involves pancreatic ducts <5 mm in diameter [2]. PanINs are usually classified into 3 stages: PanIN-1 (PanIN-1A and 1B), PanIN-2, and PanIN-3 [4], although a recent consensus report divided PanINs into 2 stages: low-grade (PanIN-1 and PanIN-2) and high-grade (PanIN-3) [5]. PanIN is presumed to be a precursor of invasive adenocarcinoma and exhibits sequential acquisition of genetic alterations and increasing cellular atypia as it progresses toward invasive disease [6].

Very few cases of synchronous SCN and other pancreatic tumours, such as neuroendocrine tumours, adenocarcinomas, and IPMNs, have been reported [7]. Neuroendocrine tumours are the most reported histological type to coexist with SCNs [7]. Notably, 20% of cases of combined SCN and neuroendocrine tumours were related to VHL disease [8]. It has been hypothesised that SCNs and neuroendocrine tumours are derived from a common ductular/centroacinar origin [8]. To our knowledge, with the exception of the present case, only 1 case of SCN coexisting with low-grade PanIN (PanIN-1 to -2) within the adjacent pancreas has been previously reported [9]. One of the characteristic features of our case was the SCN and high-grade PanIN mimicking IPMN on imaging analyses. In the present case, communication between the main pancreatic duct and the cystic lesion was suspected based on the MRP and endoscopic ultrasonography findings, though such a communication was not confirmed by ERP or in the resected material, which led to a preoperative diagnosis of IPMN. The stenosis of the main pancreatic duct on ERP and MRP led to a more specific preoperative diagnosis of IPMN coexisting with invasive ductal adenocarcinoma.

Several pancreatic diseases, such as neuroendocrine tumours and acinar cell carcinomas, can cause dilatation or cystic formation of the pancreatic duct, mimicking IPMN [10, 11]. However, there is no previous report of a case of combined SCN and PanIN mimicking IPMN, as in our present case. IPMN differs from SCN in that SCN does not usually communicate with the main pancreatic duct and there is no discharge of mucus from the ampulla of Vater. However, 9% of serous cystadenomas communicate with the main pancreatic duct

[12]. Furthermore, it is often difficult to distinguish between IPMN and other cystic lesions if enhanced mucus secretion is not apparent [13].

Regarding the molecular aspects, PanIN is associated with several genetic alterations, including in KRAS, TP53, p16/CDKN2A, and DPC4/SMAD4 [2]. In contrast, SCN shows no mutations in KRAS and p53 [14]. On the other hand, a mutation in VHL is a common alteration in both SCN and PanIN. Expression of the VHL protein is lost in 96% of PanIN cases [15], and 22% of sporadic SCN cases have been reported to have potentially inactivating mutations in the VHL gene [14]. Although it is unknown whether the SCN and PanIN in our present case occurred independently, a VHL alteration would not be a common alteration in the tumorigenesis of both SCN and PanIN, because the VHL protein was lost in PanIN but preserved in SCN immunohistochemically.

In conclusion, we here present the second case of an SCN coexisting with a high-grade PanIN mimicking IPMN. Pancreatic cystic lesions are sometimes difficult to distinguish preoperatively.

Acknowledgements

The authors would like to thank all technicians from the Division of Diagnostic Pathology, Tokai University Hospital, for their valuable technical assistance.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Warshaw AL, Compton CC, Lewandrowski K, Cardenosa G, Mueller PR: Cystic tumors of the pancreas. New clinical, radiologic, and pathologic observations in 67 patients. Ann Surg 1990;212:432–445.
2 Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, Biankin SA, Compton C, Fukushima N, Furukawa T, Goggins M, Kato Y, Klöppel G, Longnecker DS, Lüttges J, Maitra A, Offerhaus GJ, Shimizu M, Yonezawa S: An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 2004;28:977–987.
3 Friebe V, Keck T, Mattern D, Schmitt-Graeff A, Werner M, Mikami Y, Adam U, Hopt UT: Serous cystadenocarcinoma of the pancreas: management of a rare entity. Pancreas 2005;31:182–187.
4 Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, Kern SE, Klimstra DS, Klöppel G, Longnecker DS, Lüttges J, Offerhaus GJ: Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol 2001;25:579–586.
5 Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, Brosens LA, Fukushima N, Goggins M, Hruban RH, Kato Y, Klimstra DS, Klöppel G, Krasinskas A, Longnecker DS, Matthaei H, Offerhaus GJ, Shimizu M, Takaori K, Terris B, Yachida S, Esposito I, Furukawa T; Baltimore Consensus Meeting: A revised classification system and recommendations from the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. Am J Surg Pathol 2015;39:1730–1741.
6 Luttges J, Kloppel G: Precancerous conditions of pancreatic carcinoma. J Hepatobiliary Pancreat Surg 2000;7:568–574.

7 Chahal P, Saad AJ, Jeyarajah RD: An unusual case of a coexistent serous cystadenoma and intraductal papillary mucinous neoplasm of pancreas. EUS to the rescue! JOP 2011;12:244–246.
8 Blandamura S, Parenti A, Famengo B, Canesso A, Moschino P, Pasquali C, Pizzi S, Guzzardo V, Ninfo V: Three cases of pancreatic serous cystadenoma and endocrine tumour. J Clin Pathol 2007;60:278–282.
9 Kwan V, Church N, Biankin S, Norton ID, Jones DB, Falk GL: Serous cystadenoma causing biliary obstruction with synchronous pancreatic intraepithelial neoplasia. Gastrointest Endosc 2006;64:291–294.
10 Basturk O, Zamboni G, Klimstra DS, Capelli P, Andea A, Kamel NS, Adsay NV: Intraductal and papillary variants of acinar cell carcinomas: a new addition to the challenging differential diagnosis of intraductal neoplasms. Am J Surg Pathol 2007;31:363–370.
11 Kenney B, Singh G, Salem RR, Paterno F, Robert ME, Jain D: Pseudointraductal papillary mucinous neoplasia caused by microscopic periductal endocrine tumors of the pancreas: a report of 3 cases. Hum Pathol 2011;42:1034–1041.
12 Zamboni G, Hirabayashi K, Castelli P, Lennon AM: Precancerous lesions of the pancreas. Clin Gastroenterol 2013;27:299–322.
13 Tada M, Kawabe T, Arizumi M, Togawa O, Matsubara S, Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsujino T, Tateishi K, Isayama H, Toda N, Yoshida H, Omata M: Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. Clin Gastroenterol Hepatol 2006;4:1265–1270.
14 Moore PS, Zamboni G, Brighenti A, Lissandrini D, Antonello D, Capelli P, Rigaud G, Falconi M, Scarpa A: Molecular characterization of pancreatic serous microcystic adenomas: evidence for a tumor suppressor gene on chromosome 10q. Am J Surg Pathol 2001;158:317–321.
15 Lin F, Shi J, Liu H, Hull ME, Dupree W, Prichard JW, Brown RE, Zhang J, Wang HL, Schuerch C: Diagnostic utility of S100P and von Hippel-Lindau gene product (pVHL) in pancreatic adenocarcinoma – with implication of their roles in early tumorigenesis. Am J Surg Pathol 2008;32:78–91.

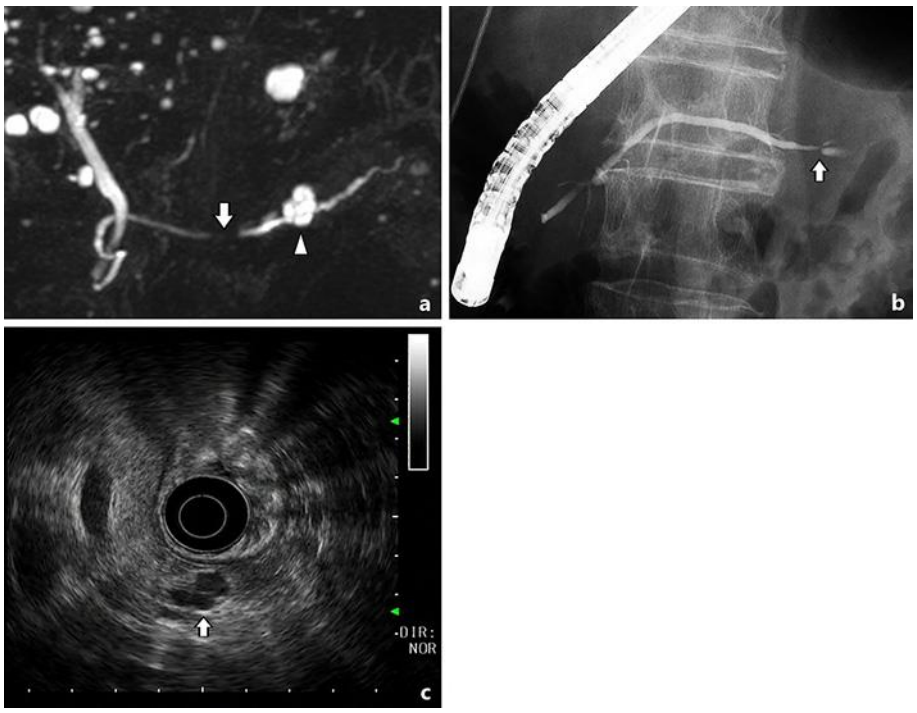

Fig. 1. **a** Magnetic resonance pancreatography shows stenosis of the main pancreatic duct (arrowhead) at the pancreatic body and dilatation of the distal side of the main pancreatic duct. A multilocular cystic lesion seems to communicate with the main pancreatic duct (arrow). **b** Endoscopic retrograde pancreatography shows stenosis of the main pancreatic duct (arrow) at the pancreatic body. **c** Endoscopic ultrasonography shows a 15-mm multilocular cystic lesion (arrow) with septal structures at the pancreatic body, whereas an intramural nodule or mass shadow was not found.

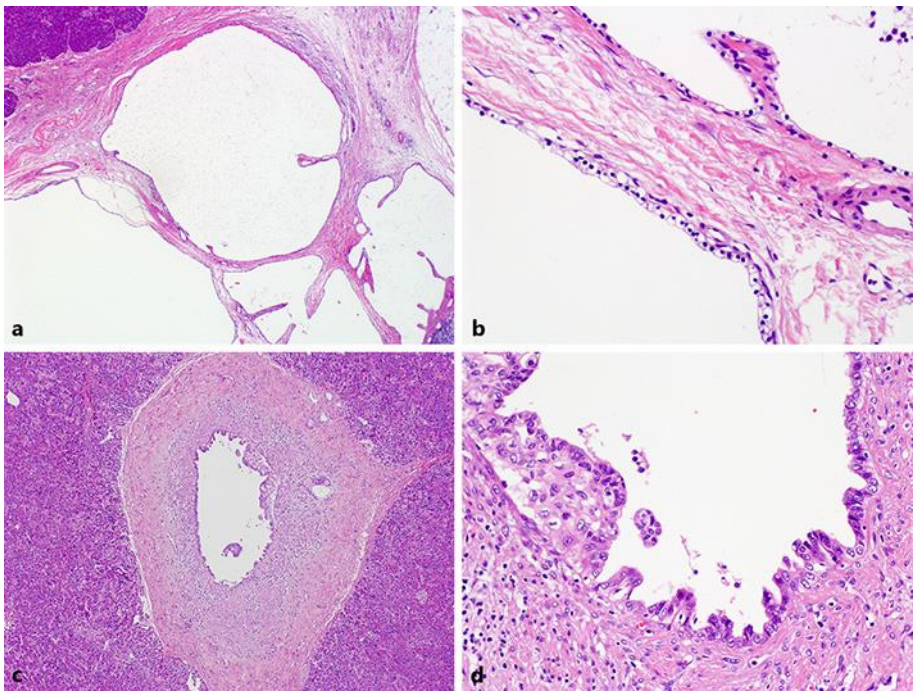

Fig. 2. Microscopic findings. **a**, **b** A cystic lesion lined with a non-atypical cuboidal or flat epithelium with clear cytoplasm is seen; this lesion was diagnosed as a serous cystic neoplasm (**a**: low-power view, **b**: high-power view). **c**, **d** High-grade pancreatic intraepithelial neoplasia lesions with stromal fibrosis are observed at the main pancreatic duct (**c**: low-power view, **d**: high-power view).

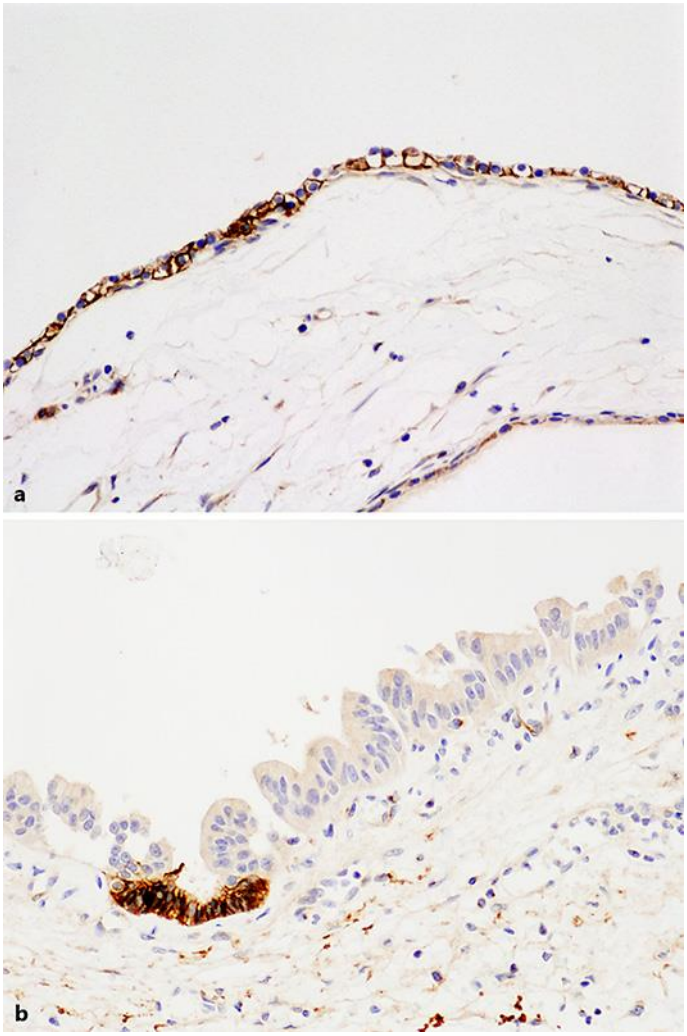

Fig. 3. Immunohistochemical findings using anti-VHL antibody. Positive anti-VHL antibody staining is observed at the epithelium of the serous cystic neoplasm (**a**), whereas negative staining is seen at the epithelium of the pancreatic intraepithelial neoplasia (**b**). VHL, von Hippel-Lindau.