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Concomitant intraductal papillary mucinous neoplasm and neuroendocrine tumor of the pancreas

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Abstract. Intraductal papillary mucinous neoplasm (IPMN) and neuroendocrine tumor (NET) of the pancreas are rare tumors and their association is not expected to be frequent. However, certain studies have suggested that the concomitant occurence of these tumors may be more frequent than previously thought. In the current study, we describe a case of concomitant occurrence of IPMN and NET of the pancreas and review the clinicopathological features of previously published cases and the current one. A 68-year-old female was incidentally found to have dilatation of the main pancreatic duct. A distal pancreatectomy was performed under the clinical diagnosis of IPMN. Histopathological analysis revealed concomitant IPMN (low-grade) and NET G1 of the pancreas. Review of the clinicopathological features of the 15 previously reported cases of concomitant IPMN and NET of the pancreas as well as the present one indicated that: i) this condition mainly affects middle-aged females; ii) the main symptom is abdominal or back pain, or no symptoms; iii) a hormone production symptom was observed in only one case; iv) the most common degree of dysplasia of IPMN is low grade; and v) the size of the NET is not particularly large (average 15.1 mm), although the clinical behavior is not always indolent (metastasis was observed in 3 cases). It is well known that IPMNs are associated with a high incidence of extrapancreatic malignancies, including colorectal and gastric carcinomas. Concomitant pancreatic NET and extrapancreatic malignancies may occur, therefore, systemic surveillance of extrapancreatic neoplasms and detection of concomitant NETs of the pancreas are necessary for patients with IPMN.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a rare intraductal epithelial neoplasm composed of mucin-producing cells arising in the main pancreatic duct or its branches (1). IPMNs are estimated to account for 1-3% of exocrine pancreatic neoplasms and 20% of all cystic neoplasms of the pancreas, and the incidence of this disease is considered to be increasing (1). The subtypes of IPMNs are recognized as main-duct and branch-duct types by macroscopic examination, and noninvasive IPMNs are classified into three categories on the basis of cytoarchitectural atypia: low-, intermediate- and high-grade dysplasia (1).

Pancreatic neuroendocrine neoplasms are uncommon and represent 1-2% of all pancreatic neoplasms (2). According to the recent World Health Organization Classification of the Digestive System, neuroendocrine neoplasms are classified into three categories: neuroendocrine tumor (NET) G1 and G2 and neuroendocrine carcinoma (NEC; NET G3) (2).

IPMN and NET of the pancreas are rare tumors and their association is not expected to be frequent. However, certain studies have suggested that the concomitant occurrence of these tumors may be more frequent than previously thought (3). In the current study, we describe a case of concomitant occurrence of IPMN and NET of the pancreas, and review the clinicopathological features of previously reported cases and the current one. The study was approved by the Ethics Committee of Shiga University of Medical Science, Shiga, Japan. Informed consent was obtained from the patient.

Patient and methods

Case report. A 68-year-old Japanese female with a past history of autoimmune hepatitis was incidentally found to have dilatation of the main pancreatic duct, measuring ~5 mm, in the pancreas tail by computed tomography (CT; Fig. 1). No other tumorous lesions were detected in the pancreas and other visceral organs by CT. No clinical symptoms of hormone overproduction were present. Under the clinical diagnosis of main-duct type IPMN, a distal pancreatectomy was performed.

The postoperative course has been uneventful, and no tumor recurrence has been observed during three years of medical follow-up.

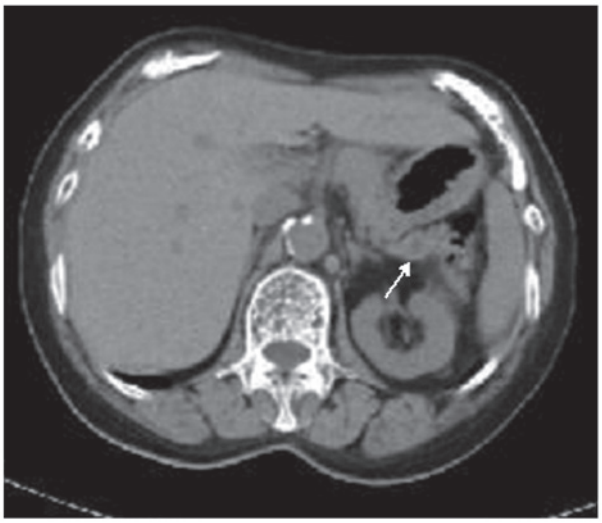

Figure 1. Dilatation of the main pancreatic duct in the pancreas tail (arrow).

Materials and methods. The formalin-fixed, paraffin-embedded tissue blocks of the resected pancreas specimens were cut into 3-μm thick sections, deparaffinized and rehydrated. Each section was stained with hematoxylin and eosin and then used for immunostaining. Immunohistochemical analyses were performed using an autostainer (Benchmark XT system; Ventana Medical System, Tucson, AZ, USA) according to the manufacturer's instructions. The following primary antibodies were used: a mouse monoclonal antibody against α-internexin (2E3; Lab Vision, Freemont, CA, USA), a mouse monoclonal antibody against chromogranin A (DAK-A3; Dako Cytomation, Glostrup, Denmark), a rabbit polyclonal antibody against gastrin (Dako Cytomation), a rabbit polyclonal antibody against glucagon (Dako Cytomation), a mouse monoclonal antibody against insulin (Z006; Nichirei Bioscience, Tokyo, Japan), a mouse monoclonal antibody against Ki-67 (MM1; Novocastra Laboratories, Ltd., Newcastle-upon-Tyne, UK), a mouse monoclonal antibody against peripherin (PJM50; Novocastra Laboratories, Ltd.), a rabbit polyclonal antibody against somatostatin receptor type 2a (SSTR2a; Gramsch Laboratories, Schwabhausen, Germany) and a mouse monoclonal antibody against synaptophysin (27G12; Novocastra Laboratories, Ltd.).

Results

Histopathological study of the resected pancreas tissue revealed dilatation and intraductal papillary proliferation of the main pancreatic duct (Fig. 2A). The epithelial cells that showed intraductal papillary proliferation were columnar and had mucin in the cytoplasm and small round nuclei with inconspicuous nucleoli (Fig. 2B). Mitotic figures were rarely observed. No invasive growth was noted. These histopathological features corresponded to IPMN with low-grade dysplasia. Well-circumscribed neoplastic growth was present in the pancreas adjacent to the IPMN (Fig. 2A and C). Trabecular growth of the neoplastic cells with eosinophilic cytoplasm and bland nuclei with inconspicuous nucleoli was observed accompanied by fibrosis (Fig. 2C and D). Mitotic figures were rarely identified (<1/10 high-power fields). No vascular invasion was noted.

Immunohistochemical analyses revealed that the neoplastic cells showing trabecular growth were diffusely positive for synaptophysin and chromogranin A (Fig. 3A). Glucagon was expressed in approximately half of the tumor cells (Fig. 3B), and a few insulin-positive tumor cells were also observed. However, gastrin positivity was not observed in any of the tumor cells. The Ki-67 labeling index was <1%. SSTR2a immunostaining was diffusely positive in the cell membrane of the tumor cells (Fig. 3C) and was score 3 according to the scoring system reported by Volante *et al* (4). No peripherin or α-internexin expression was observed in the tumor cells.

According to these histopathological and immunohistochemical findings, an ultimate diagnosis of concomitant IPMN (low-grade dysplasia) and NET G1 of the pancreas was made.

Discussion

In the current study, we describe a case of concomitant IPMN and NET of the pancreas. Table I summarizes the clinicopathological features of the 15 previously reported cases of concomitant IPMN and NET (3,5-9) as well as the present case. This condition mainly affects middle-aged females (average age, 63.1 years; range, 40-76 years; male/female ratio, 5:11). The main symptoms are abdominal or back pain (8 cases), no symptoms (5 cases) or weight loss (5 cases). A hormone production symptom (hypoglycemia) was observed in only one case. The most common degree of dysplasia of IPMN was low grade, however, high-grade dysplasia was also present (2 cases). The size of the NETs were not particularly large (average, 15.1 mm; range, 3-30), however, the clinical behavior was not always indolent. Metastasis of the NET was observed in 3 cases and one of these cases succumbed to NET; the histopathology of this case was NEC (NET G3). The preoperative clinical diagnosis was variable; IPMN in 7 cases and concomitant in 6 cases. Therefore, detailed pathological analysis of the resected pancreas tissue is required to indicate adequate treatment since metastasis of the NET may occur in some patients with concomitant IPMN and NET, even in those with small-sized lesions.

Somatostatin is an acidic polypeptide that inhibits cell proliferation and differentiation (10). The physiological action of somatostatin is initiated by its interaction with a family of receptors consisting of five different subtypes, SSTR1-5 (11). Somatostatin analogs (including octreotide) bind to the SSTRs, particularly SSTR2a, which is the most widely expressed subtype in NETs (4). A previous study revealed that somatostatin analogs significantly lengthen the time to tumor progression in patients with metastatic midgut NETs (12). Therefore, immunohistochemical analysis of SSTR2a expression in NETs is required to examine the suitability for somatostatin receptor analog treatment. Although the metastatic rate is low in NET G1, the analysis of SSTR2a expression is useful for identifying the utility of an optional treatment for the unexpected metastasis of NETs.

Expression of the intermediate filaments, peripherin and α-internexin, in NETs of the appendix and rectum has been previously reported (13,14). We have previously characterized the expression patterns of neuronal intermediate filament

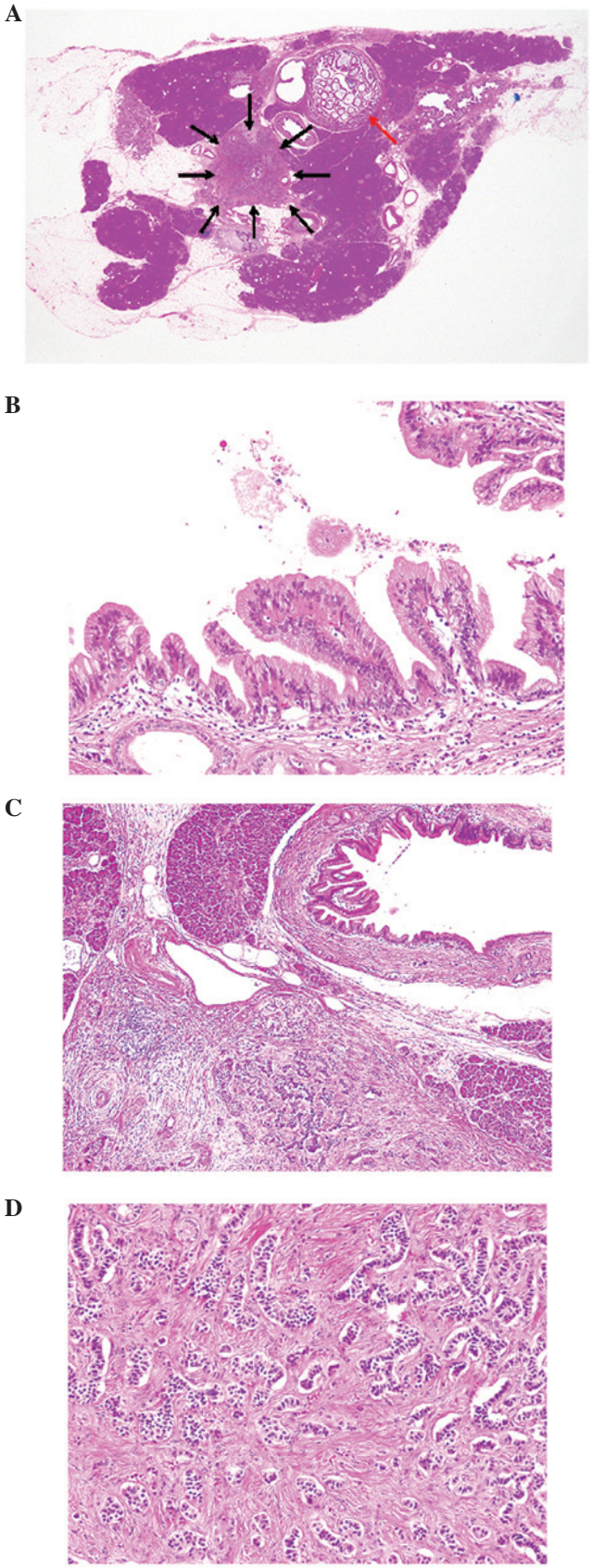

Figure 2. Histopathological findings. (A) Panoramic view of resected pancreas tissue showing dilated main pancreatic duct composed of papillary proliferation (intraductal papillary mucinous neoplasia: red arrow) and solid growth of the neuroendocrine tumor (black arrows) adjacent to main pancreatic duct (hematoxylin and eosin stain). (B) Main pancreatic duct with papillary proliferation of mucinous cells without atypia (hematoxylin and eosin stain, x200). (C and D) Neuroendocrine tumor showing trabecular growth of bland epithelial cells with fibrosis (hematoxylin and eosin stain, x40 and x200, respectively).

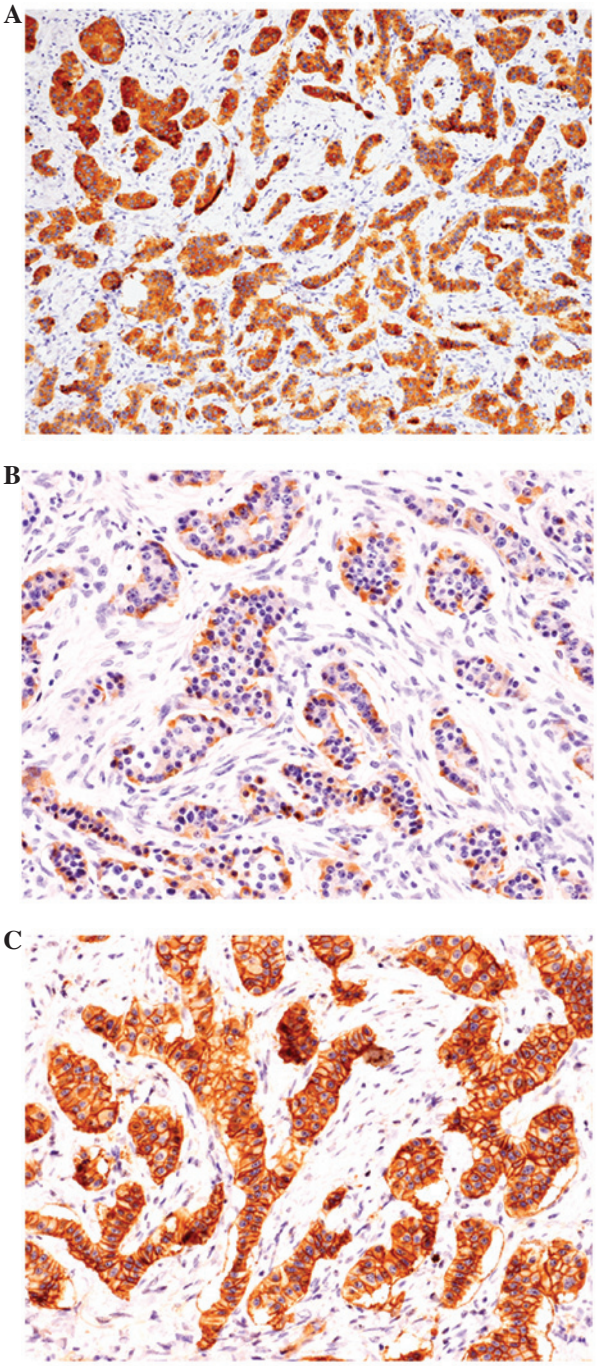

Figure 3. Immunohistochemical findings of the neuroendocrine tumor. (A) Synaptophysin is diffusely positive (x100). (B) Approximately half of the tumor cells were positive for glucagon (x200). (C) Tumor cells diffusely expressing somatostatin receptor type 2a in the cell membrane (x200).

proteins in the NETs of various organs (13,14). While peripherin (a type III intermediate filament protein expressed in normal peripheral nerves) is expressed in all NET G1 of the rectum, the frequency of its expression is low in NET G2 of the rectum (13). By contrast, the expression of α-internexin (a type IV intermediate filament protein normally found in the central nervous system) is observed in all NET G1 of the appendix and approximately half of rectal NET G1. All appendiceal NET G1 co-express peripherin and α-internexin (14). Since neither peripherin nor α-internexin expression was observed in this case of NET G1 of the pancreas, it appears

Table I. Clinicopathological features of concomitant IPMN and NET of the pancreas.

Case	Age (years) /gender	Symptom	Preoperative diagnosis	IPMN		NET			Ref.
				Type	Dysplasia	Size (mm)	Location	Behavior	
1	73/M	Left hypochondrium pain	Concomitant	Branch	Low	28	Tail	Potential malignant	3
2	40/F	Epigastric pain	Concomitant	Branch	Low	11	Head	Benign	3
3	61/F	Epigastric pain	IPMN	Branch/main	Intermediate	12	Tail	Benign	3
4	55/F	Jaundice, weight loss, epigastric pain	NET	Branch/main	Low	30	Head	Invasive, metastasis (+)	3
5	68/F	None	Concomitant	Branch/main	Low	18	Body	Benign	3
6	62/M	Epigastric pain, jaundice	IPMN	Branch/main	High	20	Head	Potential malignant	3
7	58/M	None	IPMN	Branch	Low	8	Tail	Benign	4
8	51/M	Hypoglycemia	NET	NA	Low	15	Tail	Benign	5
9	72/F	Back pain	NET	NA	Intermediate-high	25	Head	Malignant, metastasis (+)[a]	6
10	59/F	Abdominal pain	Concomitant	Branch	NA	7.8	Body	Benign	7
11	55/F	None	Concomitant	Branch	NA	20	Head	Low malignant potential	7
12	67/M	Weight loss	IPMN	Main	Low	8	Head	Well-differentiated	8
13	72/F	Abdominal pain	Concomitant	Branch	Low	16	Tail	Malignant, metastasis (+)	8
14	72/F	None	IPMN	Branch	Low	9	Body	Well-differentiated	8
15	76/F	Weight loss	IPMN	Branch	Low	11	Head	Well-differentiated	8
Present case	68/F	None	IPMN	Main	Low	3	Tail	NET G1	

IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; M, male; F, female; NA, not available. [a]Mortality from NET.

that intermediate filament protein expression varies with NET origin.

It is well known that IPMNs are associated with a high incidence of extrapancreatic malignancies, which proceed, coexist with or succeed IPMN (approximately 25-30% of IPMN cases) (15-17). Colorectal and gastric carcinomas are the most common extrapancreatic carcinomas (15-17).

In conclusion, although patients with IPMN have a favorable prognosis with a 5-year survival rate of almost 100% (16), concomitant pancreatic NET and extrapancreatic malignancies may occur, therefore, systemic surveillance of extrapancreatic neoplasms and detection of concomitant NETs of the pancreas are necessary for patients with IPMN.

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