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CASE REPORT

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Mixed ductal-endocrine carcinoma of the pancreas presenting as gastrinoma with Zollinger-Ellison syndrome: an autopsy case with a 24-year survival period

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Abstract We report an autopsy case of mixed ductal-endocrine carcinoma of the pancreas presenting as gastrinoma with Zollinger-Ellison syndrome. A 38-year-old Japanese male was found to have Zollinger-Ellison syndrome and pancreatic gastrinoma, and gastrectomy and resection of the pancreatic tumor were performed. However, hypergastrinemia persisted, and the patient died of disseminated carcinomatosis at 62 years of age, 24 years after the onset of Zollinger-Ellison syndrome. At autopsy, the main tumor was present in the residual pancreas, and metastases were noted in many organs. In the pancreas and other organs, ductal and endocrine carcinoma areas were mixed and there was a gradual transition between the two. No acinar differentiation was noted. The ductal elements were positive for mucins and carcinoembryonic antigen but negative for neuroendocrine markers, while endocrine elements were positive for chromogranin A and synaptophysin and to a lesser extent for gastrin, but negative for mucins and carcinoembryonic antigen. The ductal elements comprised about 30% of the tumor cells, and endocrine elements 70%. According to the revised World Health Organization classification, our case was diagnosed as mixed ductal-endocrine carcinoma. Our case is rare because the tumor manifested as gastrinoma with Zollinger-Ellison syndrome and the patient survived for 24 years. To the best of our knowledge, no such case has been reported. Our case suggests that pancreatic endocrine tumors may evolve into mixed ductal-endocrine carcinomas.

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Abbreviations *WHO* World Health Organization · *CEA* carcinoembryonic antigen · *CA 19-9* carbohydrate antigen 19-9

Introduction

Malignant pancreatic tumors are usually classified into those of the exocrine pancreas or those of the endocrine pancreas (Langerhans' islets). According to the revised World Health Organization (WHO) classification [7], exocrine pancreatic carcinomas were categorized into several types largely depending on the differentiation, i.e., ductal or acinar [7]. Thus, pancreatic carcinomas have been largely classified into three types – ductal, acinar and endocrine – with several peculiar variants, including cystadenocarcinoma, pancreatoblastoma, intraductal papillary-mucinous carcinoma, and solid pseudopapillary tumor [7].

Mixed ductal-endocrine carcinoma is among such histological variants and is defined as "a carcinoma in which ductal and endocrine cells are intimately admixed", according to the WHO criteria [7]. Because pancreatic ductal carcinomas frequently exhibit endocrine components [2, 3, 5, 16, 19, 25], as is the case with carcinomas in other organs [1, 24, 27], the endocrine cell component should comprise more than 30% of the tumor area in making the diagnosis of mixed ductal-endocrine carcinoma [7].

Mixed ductal-endocrine carcinoma is very rare; there have been only a few reported cases [13, 17, 20]. Here, we report an autopsy case of this carcinoma presenting as Zollinger-Ellison syndrome due to gastrinoma. The patient survived for 24 years from the onset. We believe that this mixed ductal-endocrine carcinoma evolved from a gastrinoma.

Table 1 Clinical summary of the patient. *CEA* carcinoembryonic antigen; *CA19-9* carbohydrate antigen 19-9

Age (years)	Remarks	Serum gastrin
38	Zollinger-Ellison syndrome Gastrectomy Pancreatic endocrine tumor (gastrinoma) Resection of pancreatic body and tail	358 pg/ml
38–50	Edema, hypoproteinemia, hypergastrinemia	350–680 pg/ml
50	Malabsorption, positive serectin test	1979 pg/ml
50–56	Hypergastrinemia	462–1864 pg/ml
56	Lung metastasis (gastrinoma)	10,600 pg/ml
58	Liver metastases	9672 pg/ml
59	Cholecystectomy (gall bladder mucosal adenocarcinoma)	25,342 pg/ml
62	Raised CEA and CA19-9 Died of disseminated carcinomatosis	43,500 pg/ml

Case report

Clinical summary

A 62-year-old Japanese man died of cachexia due to a disseminated carcinoma 24 years after the onset of Zollinger-Ellison syndrome due to pancreatic gastrinoma. The clinical history is summarized in Table 1.

At 38 years of age, he developed gastroduodenal ulcers, gastric acid hypersecretion, hypergastrinemia (358 pg/ml; normal 30–80 pg/ml), and an islet cell tumor of the pancreas. He was diagnosed as having Zollinger-Ellison syndrome. He underwent a total gastrectomy and resection of the pancreatic body and tail harboring the tumor (1 cm in diameter). The pancreatic tumor was an encapsulated islet cell tumor devoid of atypia, capsular invasion or venous invasion (Fig. 1A, B). A retrospective immunohistochemical study showed the presence of gastrin (Fig. 1C); thus, the tumor was diagnosed as a gastrinoma.

From then on, mild hypergastrinemia persisted and he occasionally developed edema and hypoproteinemia, but these were quite stable until 50 years of age, when leg edema, malabsorption, marked hypergastrinemia (1979 pg/ml) and anemia were observed. While residual gastrinoma was strongly suspected because a serectin test also showed a paradoxical response, imaging techniques failed to detect any tumors. From then on, he was followed up and persistent hypergastrinoma was still present.

At 56 years of age, a chest X-ray revealed a coin lesion measuring 2 cm and abdominal computed tomography showed cholecystitis. Segmentectomy of the lung harboring the mass was performed, and histological examination revealed that the lung mass was a gastrinoma positive for gastrin and neuroendocrine markers including chromogranin, synaphtophysin, and neuron-specific enolase. After the operation, his serum gastrin level fell from 10,600 pg/ml to 514 pg/ml but, thereafter, it rose to 16,500 pg/ml and the hypergastrinemia persisted. At 58 years of age, multiple liver masses were detected, and he was treated with transarterial embolization therapy. At 59 years of age, he was found to have gall stones and cholecystitis, and a cholecystectomy was performed. Histopathological examination of the gall bladder showed non-invasive, well-differentiated tubular adenocarcinoma confined to the mucosa with no vascular invasion.

His condition gradually deteriorated and, at 62 years of age, he was admitted to our University Hospital for terminal care. At this time, the tumor involved multiple organs including the lung, liver, skin and systemic lymph nodes, and serum laboratory data showed high levels of carcinoembryonic antigen (CEA) (1530 ng/ml) and high carbohydrate antigen 19-9 (CA19-9) (6400 U/ml), as well as hypergastrinemia (43,500 pg/ml). He died of cachexia at 62 years of age.

Autopsy findings

Gross findings

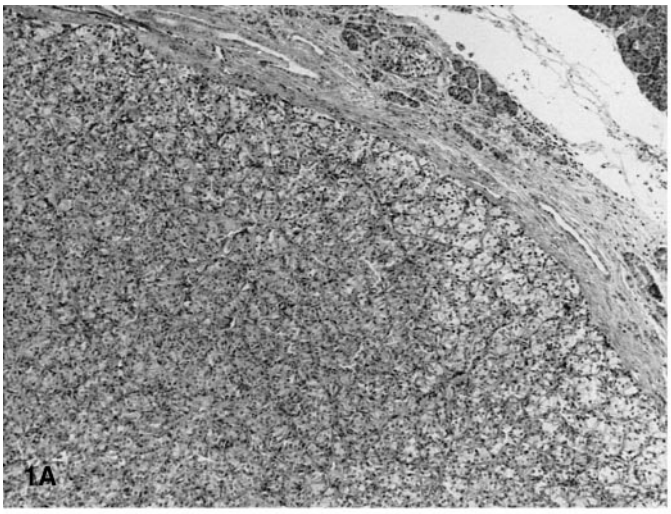
At autopsy, a large mass measuring 10×9×8 cm was found around the residual pancreas. On the cut surface of the mass, pancreatic tissue was recognized, and the peripancreatic lymph nodes were supplanted by tumor tissue. Other mass formations were recognized in the peritoneum, pericardium, lungs, small intestine, large intestine, liver, kidneys, adrenals, bone marrow, and systemic lymph nodes. Because the pancreatic mass was the largest, the primary site was considered to be the pancreas and the other masses appeared to be metastases. Other gross changes included pneumonia, pulmonary edema, pleural effusion (left, 300 ml; right, 200 ml), ascites (200 ml), congestion of kidneys, and prostatic hyperplasia. The gall bladder and spleen had been surgically resected and, therefore, these organs were not found at autopsy.

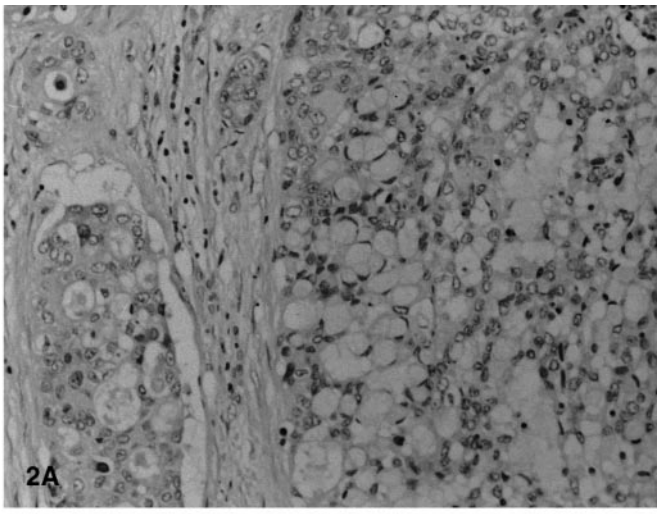
Microscopic findings

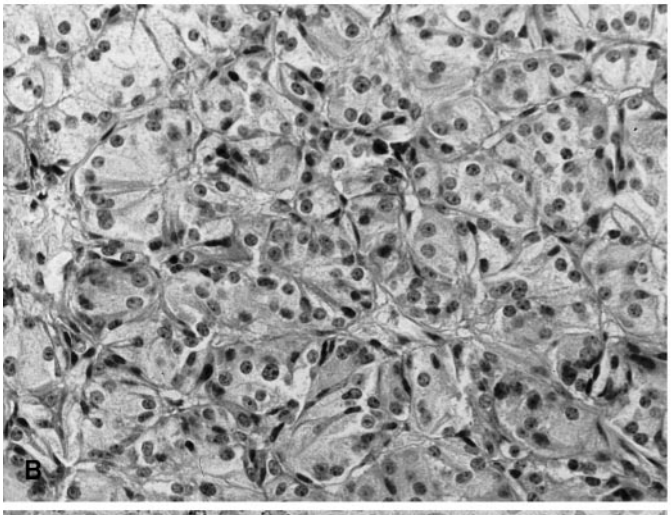
The pancreas showed the proliferation of a malignant epithelial tumor against a background of chronic tumor-associated pancreatitis. Interestingly, two populations of carcinoma cells were recognized; one was a poorly differentiated ductal adenocarcinoma and the other was a neuroendocrine carcinoma. The former formed solid cell nests, ill-defined tubules, signet ring cells or mucinous carcinomatous areas (Fig. 2A), while the latter had trabecular cell nests occasionally arranged as festoon or ribbon-like structures with rather uniform nuclei and eosinophilic cytoplasm (Fig. 2B). These two elements were mixed, and there was a gradual histological transition between the two (Fig. 2C). The metastatic lesions showed the same tumor morphology as the pancreas. The ductal carcinoma area comprised about 30% of the tumor, and the endocrine carcinoma area about 70%.

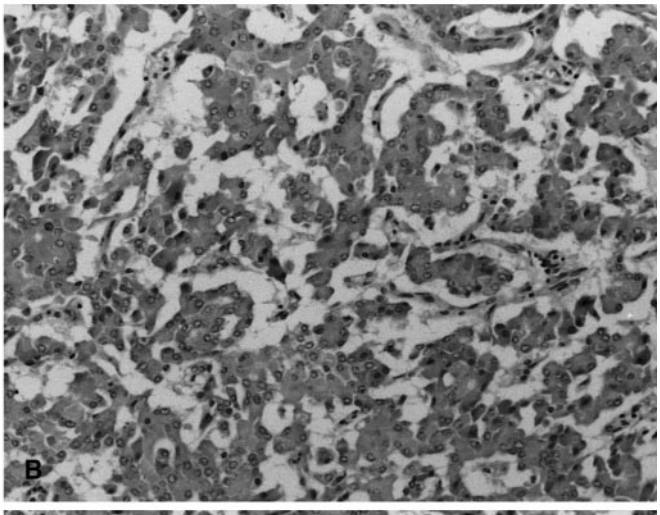
Mucin histochemistry revealed that the ductal carcinoma cells were positive for neutral and acidic mucin, as evidenced by periodic acid-Schiff after diastase digestion and by alcian blue stain at pH 2.5 (Fig. 3A), while neuroendocrine carcinoma cells were negative for mucins.

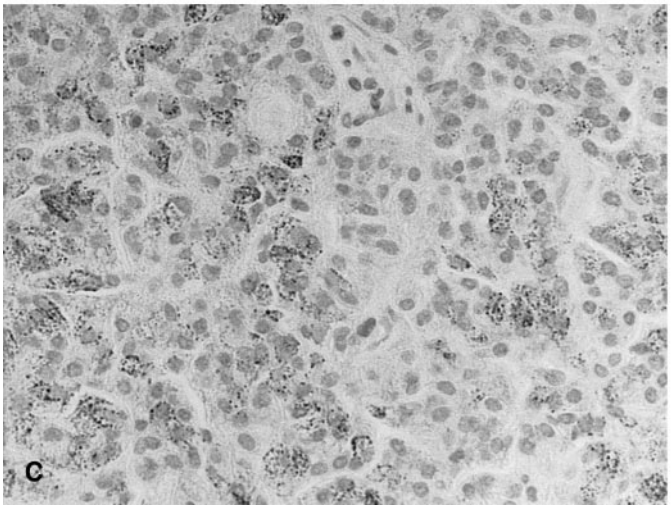
An immunohistochemical study revealed that the ductal carcinoma cells were positive for CEA (Fig. 3B), but negative for chromogranin A, synaptophysin, gastrin, glucagon, and insulin. Only infrequently were the ductal carcinoma cells positive for pancreatic lipase (Fig. 3C), trypsinogen, alpha-amylase and chymotrypsinogen. In contrast, the endocrine carcinoma cells were negative for CEA, but positive for chromogranin A (Fig. 4A) and to a lesser extent for synaptophysin. Immunoreactive gastrin was also noted in the endocrine carcinoma cells (Fig. 4B), although positive cells were sparse. No immunoreactivities for glucagon, insulin, pancreatic lipase, trypsinogen, alpha-amylase and chymotrypsinogen were observed in the endocrine carcinoma cells.











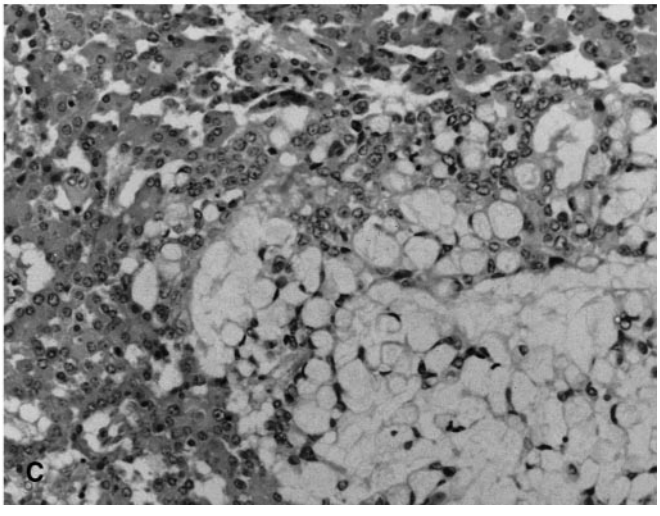
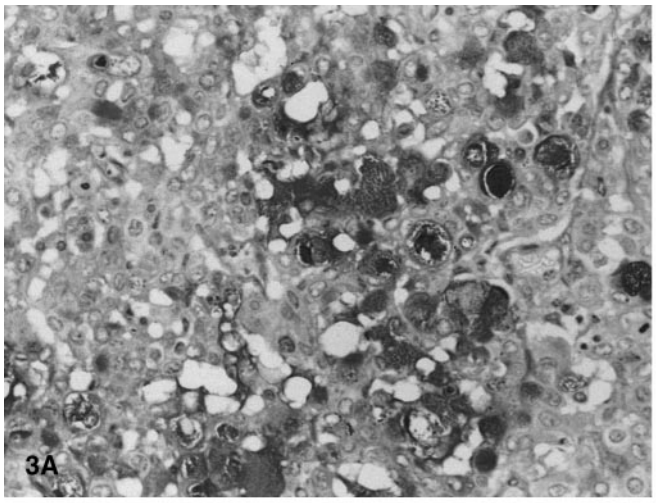
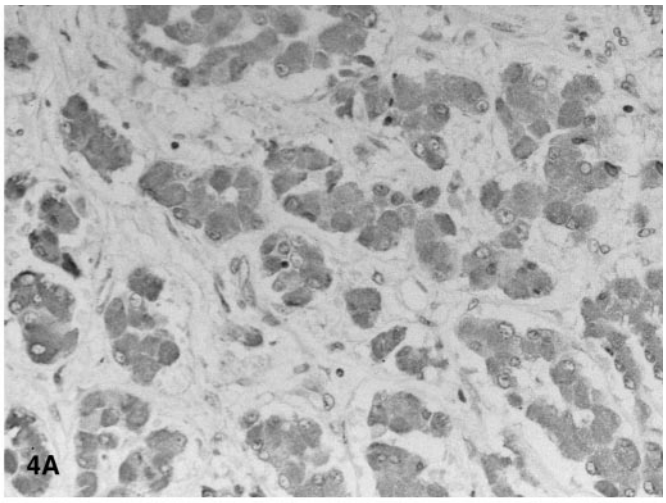
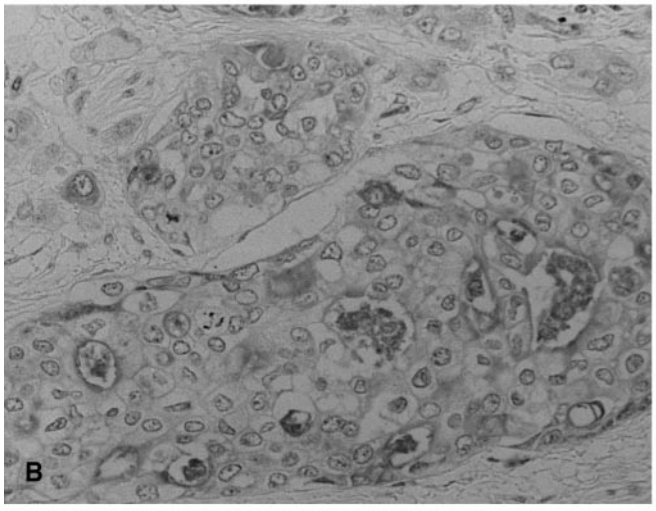


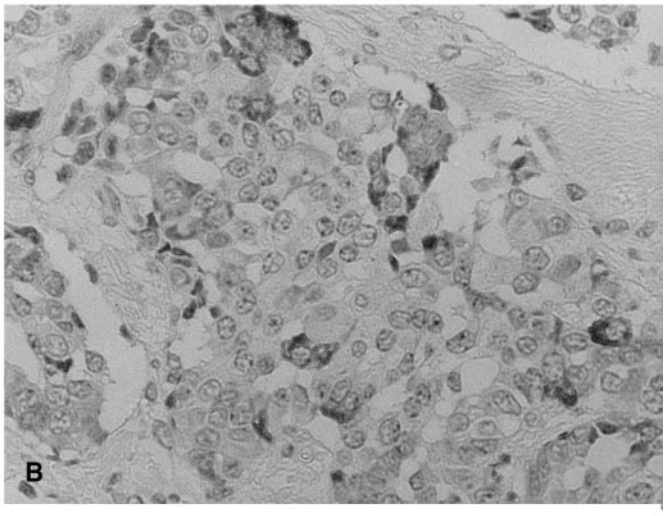
Fig. 1 Islet cell tumor resected at 38 years of age. **A** Low-power view shows encapsulated endocrine tumor without capsular penetration and vascular invasion. Hematoxylin and Eosin ×150. **B** High-power view shows that the tumor is an endocrine tumor, cells of which are free of atypia and arranged with trabecular pattern separated by endothelial cells. Hematoxylin and Eosin ×300. **C** A retrospective immunohistochemical study demonstrates the presence of immunoreactive gastrin. Immunostain for gastrin ×330

Fig. 2. Histological features at autopsy. **A** Ductal adenocarcinomatous area of the pancreatic tumor. There are tubular formation (*left*) and mucinous area (*right*). Hematoxylin and Eosin ×250. **B** Endocrine carcinomatous area of the pancreatic tumor. The endocrine carcinomatous cells were composed of eosinophilic cells arranged with trabecular and ribbon-like patterns. The nuclei are rather uniform. Hematoxylin and Eosin ×250. **C** The pancreatic tumor consists of ductal carcinomatous area with mucin (*right*) and endocrine carcinomatous area (*left*). These elements are intimately admixed. Hematoxylin and Eosin ×250









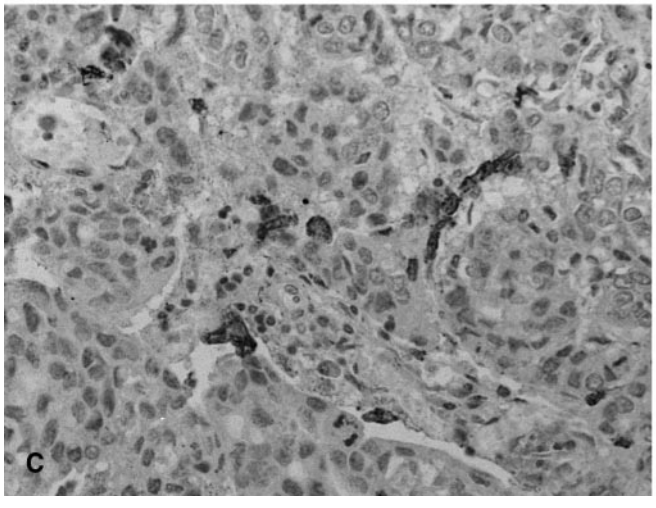


Fig. 3 The ductal carcinomatous area of the pancreatic tumor. **A** Mucins are noted. PAS with diastase digestion ×300. **B** Carcinoembryonic antigen is positive. Immunostain ×300. **C** Pancreatic lipase-positive cells are sparsely scattered. Immunostain ×300

Fig. 4 The endocrine carcinomatous area of the pancreatic tumor. **A** Chromogranin A is positive. Immunostain ×350. **B** Gastrin-positive cells are scattered. Immunostain ×300

The residual pancreas showed chronic tumor-associated pancreatitis with Langerhans' islet hyperplasia. Immunoreactivities for chromogranin A, synaptophysin, gastrin, insulin, and gastrin were noted in the hyperplastic Langerhans' islet cells. Other pathological changes included edema and bronchopneumonia of the bilateral lungs, prostatic hyperplasia, and chronic cystitis of the urinary bladder. No residual gall bladder carcinoma was recognized. The cause of death was considered to be cachexia due to extensive tumor dissemination.

Discussion

At autopsy, we diagnosed this case as mixed ductal-endocrine carcinoma of the pancreas because our case fulfilled the criteria of the revised WHO classification 7]. It has been reported that pancreatic ductal carcinomas may contain endocrine components [2, 3, 5, 16, 19, 25], and

such ductal carcinomas pose a diagnostic problem [16]. In such ductal carcinomas with endocrine components, endocrine cells are scattered among or under the tubules of ductal carcinoma cells and do not have the histology of an endocrine carcinoma [2, 3, 5, 16, 19, 25]. In addition, endocrine cells comprise only a small population, less than 30% of tumor cells [2, 3, 5, 16, 19, 25]. In our case, both ductal carcinoma and endocrine carcinoma were mixed and the endocrine carcinomatous area occupied approximately 70% of the total tumor area, indicating that our case was not a ductal carcinoma with endocrine components. The adenocarcinomatous areas of our tumor were not metastases from the gall bladder intramucosal adenocarcinoma resected at 59 years of age, because their histologies were different and because the ductal carcinoma areas of the tumor were intimately admixed with the endocrine carcinoma areas.

There are other mixed variants of pancreatic tumors, such as mixed acinar-endocrine [7, 26] and mixed ductal-acinar-endocrine [14, 21] tumors. Our case lacked acinar differentiation. In this respect, in our case, pancreatic digestive enzymes were infrequently immunoreactive in the ductal carcinoma area. In a previous study, including molecular analysis. benign and malignant tumors of the gastrointestinal organs, including pancreatic ductal carcinoma, occasionally expressed pancreatic digestive enzymes [23]. In addition, Kim et al. [6] demonstrated the presence of immunoreactive pancreatic digestive enzymes in 17% of pancreatic ductal carcinomas, and Ohta et al. [15] demonstrated the presence of immunoreactive pancreatic digestive enzymes in normal pancreatic ducts. These studies indicate that pancreatic enzyme immunoreactivity is not a specific marker of acinar differentiation in pancreatic cancers. We think that careful examination of both histology and immunohistochemistry of pancreatic digestive enzymes are necessary for the evaluation of acinar differentiation. Therefore, positive immunoreactivities for pancreatic enzymes in the ductal carcinoma area in our tumor do not indicate acinar differentiation.

It is of particular interest that our case presented as an endocrine tumor (gastrinoma with Zollinger-Ellison syndrome) and terminated as a mixed ductal-endocrine carcinoma, suggesting that pancreatic endocrine tumors may evolve into mixed ductal-endocrine carcinomas. Although the mechanism is unclear, the ductal elements in our tumor may have arisen from pre-existing gastrinoma cells. In this respect, ductal, acinar, and endocrine cells in the pancreas share a common cell origin during the fetal development [4, 9, 22]. Pancreatic ductal cells in human adults may be able to differentiate into endocrine cells and acinar cells [4, 9]. In addition, ductular cells are able to differentiate into both endocrine and ductal structures in experimental carcinogenesis of rodents [18, 19]. These findings suggest that differentiation from ductal cells or ductular cells into endocrine cells may occur. However, de-differentiation from endocrine cells to ductal cells has not been demonstrated, to the best of our knowledge. Our case strongly suggests that de-differentiation from endocrine tumor cells into ductal carcinoma cells does occur in human pancreatic carcinogenesis, thus leading to mixed ductal-endocrine carcinoma as in our case.

It is also of particular interest that the patient survived for 24 years. Approximately 80% of gastrinomas are malignant. In our case, the endocrine tumor at 38 years of age was encapsulated and devoid of cellular atypia, capsular invasion or vascular invasion, suggesting the benign nature of the tumor.

Hypergastrinemia persisted for as long as 24 years from the initial tumor resection, suggesting that residual gastrinoma cells were present. Lung metastasis was first observed at 56 years of age, 16 years after the initial onset. This suggests that the tumor was a very low grade malignant tumor from the onset or underwent malignant transformation during the clinical course. The patient survived a further 6 years. During the terminal stage, serum CEA and CA19-9 showed high values, indicating that de-differentiation from endocrine cells to ductal cells occurred in the late stage, or that it simply signified an increase in the mass of the existing ductal carcinoma component. From these findings, we conclude that the endocrine tumor was at first benign or very low grade malignant, and during the long clinical course the tumor underwent malignant transformation or progression, probably due to genetic alterations.

Recent molecular studies have indicated that pancreatic endocrine tumors may be an oligoclonal origin [10, 11, 12]. This has been investigated using molecular nucleic acid techniques, such as chromosome analysis [10], loss of heterozygosity analysis of a particular gene [11], or polymerase chain reaction-based techniques [12]. In our tumor, no genetic molecular analysis was performed. Immunohistochemically, the endocrine component was positive for gastrin but negative for insulin and glucagon, suggesting that the endocrine component of our tumor was monoclonal at the protein level.

Finally, the residual pancreas contained hyperplastic islets with gastrin immunoreactivity. The hyperplastic islets seemed to be the result of the previous pancreatic resection. Although the reason for the gastrin immunoreactivity in the residual islets is unclear, we believe that the hypergastrinemia was not so marked as to cause complete deletion of gastrin cells, or that islet hyperplasia type I occurred in our case, as suggested by Larsson [8].

In summary, our case suggests that pure pancreatic endocrine tumors may transform into mixed ductal-endocrine carcinomas after a long interval.

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