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Endocrine cells in intraductal papillary-mucinous neoplasms of the pancreas

A histochemical and immunohistochemical study

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Abstract The endocrine cells in intraductal papillary-mucinous neoplasms (IPN) of the pancreas have rarely been investigated. In the normal pancreatic ducts of normal pancreases (*n*=5) there were a few endocrine cells: argyrophil in 5 (100%), chromogranin A in (100%), pancreatic polypeptide (PP) in 3 (60%), and insulin in 7 (20%). These endocrine cells were scattered, and located in the basal portions of pancreatic ducts. In IPN of the pancreas (*n*=9), there were many endocrine cells: argyrophil in 7 (78%), argentaffin in 8 (89%), chromogranin A in 8 (89%), PP in 7 (78%), serotonin in 7 (78%), insulin in 4 (44%), and gastrin in 5 (56%). In invasive ductal adenocarcinoma of the pancreas (*n*=6), many endocrine cells were also detected: argyrophil cells in (67%), chromogranin A in 3 (50%), insulin in 3 (50%), glucagon in 4 (67%), and somatostatin in 3 (50%). In positive cases, endocrine cells were situated under or among the neoplastic cells and the proportion of endocrine cells in IPN was less than 5% of the total neoplastic cell population. These data show that normal pancreatic ducts contain endocrine cells and that IPN frequently contain argyrophil, argentaffin, chromogranin A, and hormone-containing endocrine cells. These data also suggest that endocrine differentiation occurs during neoplastic transformation and progression of IPN of the pancreas.

Introduction

As neuron and endocrine cells have been found to have many common features, the term “neuroendocrine” has been applied to them [6], though they have been found in many organs other than the endocrine glands. They have common histochemical features, including amino uptake, serotonin positivity, and affinity to potassium dichromate (chromaffin) [6], and characteristically have an affinity to silver. Electron microscopy and immunohistochemistry have revealed that these cells have characteristic secretory granules and also contain various peptide hormones [6]. Endocrine cells are present among the normal cells of non-endocrine organs as well as in cancerous non-endocrine organs [3]. These cells secrete several hormones that regulate cell growth and differentiation via autocrine and/or paracrine loops [5, 21, 28]. The receptors for these hormones are also present in cells of the non-endocrine organs [14, 34]. In the exocrine pancreas, endocrine cells have been reported to be present in the pancreatic ducts of the normal pancreas and pancreases affected by chronic pancreatitis [2, 4, 30] as well as in pancreatic ductal carcinomas [2, 4, 7, 9, 11, 22, 30].

Intraductal papillary-mucinous neoplasm (IPN) of the pancreas is a rare and unique form of pancreatic neoplasm. It is characterized by intraductal papillary epithelial proliferations with dilatation of the main pancreatic duct and/or its major branches [1, 8, 13, 16–19, 23–27, 29, 31–33, 36]. A large amount of mucin usually fills the dilated pancreatic ducts. IPN usually shows a benign clinical course, but malignant transformation has been reported [1, 8, 13, 16–19, 23–27, 29, 31–33, 36]. Histopathologically, IPN shows variable histology, ranging from tall, highly differentiated, columnar mucin-containing cells to carcinoma in situ [1, 8, 13, 16–19, 23–27, 29, 31–33, 36], which reflects its variable biological behaviour. In the recent revised WHO classification [10], IPN was classified as benign, borderline and malignant. Much effort has been devoted to characterization of this neoplasm. It has been shown that IPN occasionally expresses oncofetal antigens [17, 18, 26, 29, 31, 32] and has altered MUC apomucin expression [33]. In addition, abnormalities of oncogenes and anti-oncogenes have been reported in IPN [13, 26, 29, 32]. However, endocrine cells have rarely been reported in IPN [16–19].

In this study, therefore, we investigated the distribution of argyrophil and argentaffin cells by histochemistry

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and examined chromogranin A-positive cells by immunohistochemistrly in normal pancreatic ducts, IPN and invasive ductal adenocarcinoma of the pancreas. In addition, we investigated several gut hormones immunohistochemically to find what kind of gut hormones are present in the endocrine cells.

Materials and methods

We collected nine cases of IPN of the pancreas from autopsy (three) and surgical (six) cases seen at our laboratories and affiliated hospitals during 1986–1995 (Table 1). According to the revised WHO classification [10], cases 1–4 in Table 1 were classified as intraductal palillary-mucinous adenoma, cases 5–7, as intraductal papillary-mucinous adenoma with moderate atypia, case 8, as intraductal papillary-mucinos carcinoma (non-invasive), and case 9, as invasive intraductal papillary-mucinous carcinoma.

We also obtained five normal pancreases from recent autopsy files at our laboratorties and six invasive ductal adenocarcinomas of the pancreas from recent surgical files. Many tissue specimens were obtained from each pancreatic specimen; they were fixed in 10% formalin and embedded in paraffin. Several 3-μm sections were obtained from each paraffin block. One of them was stained with haematoxylin and eosin, and two with Grimelius' technique for argyrophil cells and with Masson-Fontana's technique for argentaffin cells. The rest were subjected to immunohistochemical study for chromogranin A and several gut hormones.

Chromogranin A and several gut hormones (Table 2) were stained immunohistochemically by the standard avidin-biotin-peroxidase complex (ABC) method. In brief, after deparaffinization, endogenous peroxidase activity was abolished in 100% methanol containing 0.3% H_2O_2. The sections were then treated at 4° C overnight with antibody solution as described in Table 2. The anti-chromogranin A reacts with a 68-kDa protein that is associated with endocrine secretory granules [35]. The sections were then treated with secondary biotinylated antibodies (Vector Lab, Berlingame, Calif.) for 2 h, followed by treatment with the ABC (Vectastein ABC Elite Kit, Vactor Lab) for 1 h. Reaction products were developed by immersing the sections in 3,3′-diaminobenzidine tetrahydrochloride solution containing 0.03% H_2O_2. Nuclei were lightly counterstained with haematoxylin. Reactions products were not present when nonimmune serum or phosphate-buffered saline was used instead of the primary antibodies.

Endocrine cells positive with Grimelius' and Masson-Fontana' stains were termed argyrophil and argentaffin cells, respectively. Endocrine cells positive for chromogranin A, a 68-kDa protein associated with endocrine secretory granules [35], were termed as chromogranin A cells. Endocrine cells positive for individual gut hormones were collectively termed hormone-containing cells, and they were subclassified as pancreatic polypeptide (PP), serotonin, insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal polypeptide (VIP) cells.

Results

The results are summarized in Table 1.

Argyrophil cells were scattered in the pancreatic ducts in all normal pancreases (Fig. 1A), but no argentaffin cells were found in any of these cases. Chromogranin A cells were scattered in the pancreatic ducts in all cases (Fig. 1B). PP and insulin cells were also scattered in three (60%) and one (20%) of the normal cases, respectively (Table 1). However, there were no serotonin, gastrin, glucagon, VIP, and somatostatin cells. The argyrophil, chromogranin A, PP or insulin cells accounted for

Table 1 Endocrine cells in normal pancreatic ducts, intraductal papillary-mucinous neoplasm of the pancreas, and pancreatic invasive ductal adenocarcinoma (*M*, male, – negative, +positive, *PP* pancreatic polypeptide, *VIP* vasoactive intestinal polypeptide; Figures in parentheses before sex show age in years)

Endocrine cells	Normal pancreas (*n*=5)	Intraductal papillary-mucinous neoplasm									Invasive ductal adenocarcinoma (*n*=6)
		Case 1 (71, M)	Case 2 (62, M)	Case 3 (91, M)	Case 4 (59, M)	Case 5 (69, M)	Case 6 (62, M)	Case 7 (72, M)	Case 8 (72, M)	Case 9 (81, M)	Total	
Argyrophil	5/5 (100%)	+	+	–	+	–	+	+	+	+	7/9 (78%)	4/6 (67%)
Argentaffin	0/5 (0%)	+	+	–	+	+	+	+	+	+	8/9 (89%)	0/6 (0%)
Chromogranin A	5/5 (100%)	+	+	–	+	+	+	+	+	+	8/9 (89%)	3/6 (50%)
PP	3/5 (60%)	–	+	+	+	–	+	+	+	+	7/9 (78%)	0/6 (0%)
Serotonin	0/5 (0%)	+	+	–	–	+	+	+	+	+	7/9 (78%)	0/6 (6%)
Insulin	1/5 (20%)	–	+	+	–	+	+	–	–	–	4/9 (44%)	3/6 (50%)
Gastrin	0/5 (0%)	–	+	–	+	–	+	–	+	+	5/9 (56%)	0/6 (0%)
Glucagon	0/5 (0%)	–	–	–	–	–	–	–	–	–	0/9 (0%)	4/6 (67%)
Somatostatin	0/5 (0%)	–	–	–	–	–	–	–	–	–	0/9 (0%)	0/6 (0%)
VIP	0/5 (0%)	–	–	–	–	–	–	–	–	–	0/9 (0%)	3/6 (50%)

Table 2 Primary antibodies used in the present study (*M/P* monoclonal/polyclonal, *PP* pancreatic polypeptide, *VIP* vasoactive intestinal polyptide)

Antibodies	M/P	Source	Dilution
Chromogranin A (LK2H10)	M	Immunotech, Marseille, France	×1
PP	P	BioGenex, Dublin, Ireland	×1
Serotonin	M	Dakopatts, Glostrup, Denmark	×50
Insulin	P	Dakopatts, Glostrup, Denmark	×200
Gastrin	P	Dakopatts, Glostrup, Denmark	×250
Glucagon	P	Dakopatts, Glostrup, Denmark	×150
Somatostatin	P	Dakopatts, Glostrup, Denmark	×300
VIP	P	BioGenex, Dublin, Ireland	×1

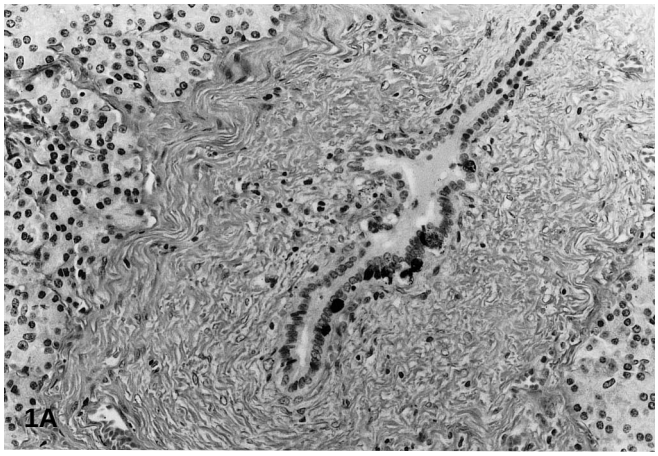
less than 3% of the total pancreatic duct cell population. The density of the endocrine cells was higher in large pancreatic ducts than in small pancreatic ducts and ductules.

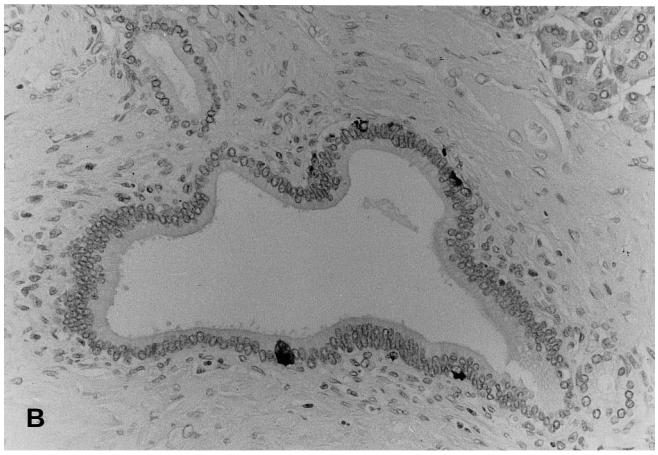
In the nine IPNs of the pancreas, the main pancreatic duct and/or its major branches were severly dilated with proliferations of the duct cells (Fig. 2). Argyrophil (Fig. 3A), argentaffin (Fig. 3B) and chromgranin A cells (Fig. 3C) were present in seven (78%), eight (89%) and eight (89%) of th IPNs, respectively (Table 2). There were many hormone-containing cells; PP cells in seven cases, or 78% (Fig. 3D), serotonin cells in seven, or 78% (Fig. 3E), insulin cells in four, or 44% (Fig. 3F), and gastrin cells in five, or 56% (Fig. 3G). There were no glucagon, VIP or somatostatin cells. In positive cases, these endocrine cells were situated under or among the neoplastic cells, and the endocrine cells accounted for less than 5% of the total neoplastic cell population.

In invasive ductal adenocarcinoma of the pancreas, argyrophil (Fig. 4A), argentaffin and chromogranin A cells (Fig. 4B) were present in four (67%), none (0%) and three (50%) of the six cases, respectively (Table 1). There were also hormone-containing cells; insulin cells in three (50%), glucagon cells in four (67%) and somatostatin cells in three (50%). There was no immunoreactivity of PP, serotonin, gastrin or VIP in cancer cells in any of these cases. In positive cases, the argyrophil, chromogranin and hormone-containing cells were located under or among the carcinoma cells, and these endocrine clls made up a proportion ranging approximately from 5% to 50% of the total carcinoma cell population. In the cancerous stroma there were endocrine cells that were considered to the residual islet cells.

Discussion

Endocrine cells have been recognized by their affinity to silver (argyrophil and argentaffin) and by immunhistochemical demonstration of chromogranin A, a 68-kDa protein associated with secretory granules [35]. Recent advances in immunohistochemistry have made it possible to reveal the hormones that are produced in the cells of the gut [6]. We examined argyrophil, argentaffin and





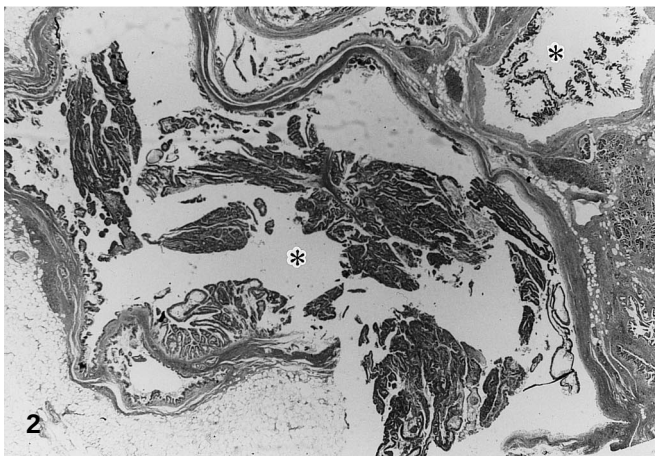


Fig. 1A, B Endocrine cells in the normal pancreatic duct of the normal pancreas. **A** Argyrophil and **B** chromogranin A cells are scattered in the basal portion of the epithelium of the normal pancreatic duct. **A** Grimelius stain, ×200. **B** Immunostaining for chromogranin A, ×200

Fig. 2 Low-power microscopic features of an intraductal papillary-mucinous neoplasm of the pancreas. The main pancreatic ducts (*asterisks*) are grossly dilated, and there are polyp-like protrusions within the pancreatic ducts. Haematoxylin and eosin,×20

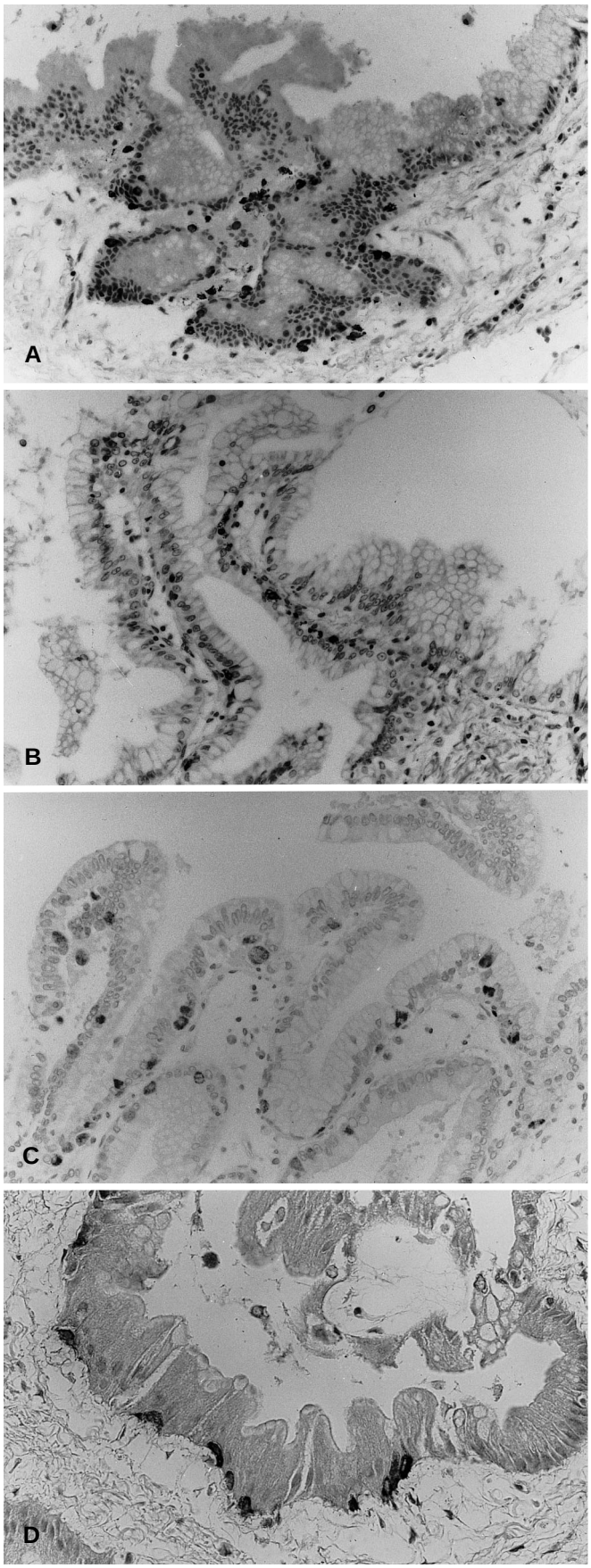


Fig. 3A–G Endocrine cells in intraductal papillary mucinous neoplasm of the pancreas. **A** Argyrophil, **B** argentaffin, **C** chromogranin A **D** pancreatic polypeptide, **E** serotonin, **F** insulin and **G** gastrin cells are scattered under or among the proliferated epithelia. **A** Grimelius stain, ×200. **B** Masson-Fontana stain, ×200. **C** Immunostaining for chromogranin A, ×200. **D** Immunostaining for pancreatic polypeptide, ×300. **E** Immunostaining for serotonin, ×300. **F** Immunostaining for insulin, ×300**. G** Immunostaining for gastrin, ×300

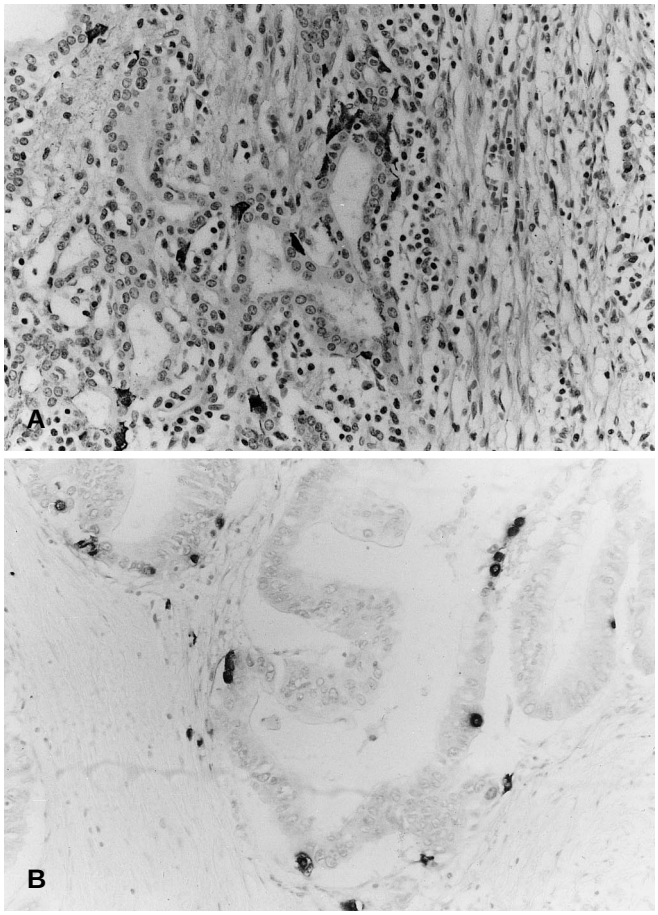


Fig. 4A, B Endocrine cells in invasive ductal adenocarcinoma of the pancreas. **A** Argyrophil and **B** chromogranin A cells are scattered under or among the carcinoma cells. **A** Grimelius stain, ×200. **B** Immunostaining for chromogranin A, ×200

chromogranin A cells, and also gut hormones. A high prevalence of endocrine cells was demonstrated by argyrophil staining and immunohistochemical staining for chromogranin A, PP, and serotonin, suggesting that these stains are useful for the detection of endocrine cells in the pancreatic ducts and their lesions.

In this study, the percentage of chromogranin A-positive cells was very similar to that of argyrophil cells in normal pancreas, IPN and invasive ductal adenocarcinoma. In this regard, Rindi et al. [24], using histochemistry, immunohistochemistry and dot-blot techniques, demonstrated that argyrophil cells reacted with chromogranin A antibody and that there was a close relationship between chromogranin A and argyrophil cells. This result was confirmed by Lundqvist et al. [15], who demonstrated using histochemistry and dot-blot studies that chromogranin A caused an argyrophil but not an argentaffin reaction. These observations may indicate that argyrophil and chromogranin A cells are the same, which might explain the similar incidence of argyrophil cells and chromogranin A cells in the present study.

Our study revealed that argyrophil, chromogranin, PP and insulin cells were scattered in normal pancreatic ducts. These findings are compatible with previous studies [2, 4, 30] and indicate that endocrine cells are present in the pancreatic duct system under normal conditions. The presence of these cells in normal ducts may contribute to the maintenance of the microenvironment of pancreatic ducts under normal conditions. We found no argentaffin, serotonin, gastrin, glucagon, VIP or somatostatin cells in the normal pancreatic ducts. In general, endocrine cells and their neoplasms (carcinoid tumour) of foregut organs are argyrophil but not argentaffin [12]. This may explain why argentaffin cells were not present in normal pancreatic ducts. The reason for the absence of other hormones is not clear.

The present study showed that argyrophil, argentaffin and chromogranin A cells were present in many cases of IPN. In addition, there were many hormone-containing cells in IPN. There have been few reports on the endocrine cells of IPN, and there have been no systematic studies on endocrine cells in IPN. Milchgrub et al. [16] mentioned that argyrophil and serotonin cells were present in one of four cases of IPN, Nishihara et al. [19] noted the presence of endocrine cells in one of two IPNs, and Nagai et al. [18] reported the presence of serotonin and chromogranin A cells. Our data show that most IPNs of the pancreas harbour endocrine cells. The origin of these cells is obscure; they may be pre-existing endocrine cells or, alternatively, they may be the result of endocrine differentiation of IPN. The latter explanation seems more likely, as no argentaffin, serotonin or gastrin cells were present in normal pancreatic ducts, while such cells were found in IPN. Although the function of endocrine cells in IPN is not known, it seems possible that hormones secreted from the endocrine cells may regulate tumour cell growth via an autocrine and/or paracrine loop, as is suspected in other tumours [5, 21, 28]. However, the role of endocrine cells in IPN may be limited as they occupied less than 5% of the total neoplastic cell population.

Argyrophil and chromogranin A cells were frequently present in cases of invasive ductal adenocarcinoma of the pancreas. In addition, there were many hormone-containing cells in cases of invasive ductal adenocarcinoma. The presence of these endocrine cells has already been described [2, 4, 7, 9, 11, 22, 30]. In our series, there was not even one case of a ductal adenocarcinoma that contained argentaffin cells, suggesting that transdifferentiation to argentaffin cells does not occur in ductal adenocarcinoma of the pancreas. The endocrine cells in ductal adenocarcinoma might arise through endocrine differentiation of carcinoma cells, as previously reported in various malignant neoplasms [3, 20]. Alternatively, however, these endocrine cells may be non-neoplastic; in several cancers endocrine cells have no proliferative activity [20] and are usually absent from metastases. The hormones secreted from endocrine cells may influence carcinoma cell growth in pancreatic ductal adenocarcinoma.

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