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# Mixed Acinar-Endocrine Carcinoma of the Pancreas
## — A Case Report —

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*A case of pancreatic carcinoma with both acinar and endocrine features is presented. The patient was a 52-year-old female presenting with jaundice of 3 weeks' duration. The tumor was a 6 × 6 cm-sized round solid mass in the head of pancreas, invading the superior mesenteric vein. Histologically, it was composed of monotonous ovoid cells with eosinophilic granular cytoplasm in solid nests and sheets with occasional acinar and glandular differentiation. Immunohistochemical study revealed coexpression of acinar and endocrine markers; amylase, chromogranin, neuron-specific enolase, glucagon, somatostatin, and gastrin in tumor cells. This is the first documented case of mixed acinar-endocrine carcinoma of the pancreas in Korea, and its amphicrine nature reflects a close histogenetic relationship between pancreatic exocrine and endocrine cells.*

**Key Words**: *Pancreas, Acinar cell carcinoma, Islet cell tumor, Exocrine, Endocrine, Amphicrine*

## INTRODUCTION

Acinar cell carcinomas and endocrine (islet cell) tumors of the pancreas have been traditionally considered as distinct types of pancreatic neoplasms in spite of their clinico-pathologic similarities. However, not a few pancreatic carcinomas with both exocrine and endocrine features, based on immunohistochemical and ultrastructural studies, have been reported in recent decades (Schron and Mendelsohn, 1984; Pour et al., 1993; Klimstra et al., 1994). We report the first documented case of mixed acinar-endocrine carcinoma of the pancreas in Korea with its clinico-pathologic and immunohistochemical findings, and discuss the histogenesis.

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## CASE REPORT

A 52-year-old female presented in September 1994 with jaundice of 3 weeks' duration. Abdomen CT scan revealed a large lobular solid mass in the head of pancreas invading the adjacent superior mesenteric vein (SMV) and distal common bile duct (CBD). The patient was normal by physical examination except for jaundice, and laboratory tests showed elevated serum levels of total and direct bilirubin, hepatic transaminases, alkaline phosphatase, glucose and cholesterol. Percutaneous transbiliary drainage (PTBD) and percutaneous gun biopsy of the tumor were performed. At operation, a 5 × 3 cm-sized well demarcated round tumor was found in the uncinate process of pancreas, invading the lateral and posterior wall of SMV. Whipple's operation with partial resection of SMV was done. The post-operative course was uneventful, and the patient has been well for 1 year.

## PATHOLOGIC FINDINGS

The resected pancreatic tumor was grossly well circumscribed, but not encapsulated, and measured 6 × 6 cm. Cut surface was homogeneously solid, yellowish white, and granular. The tumor was protruding into the dilated lumen of distal CBD. On microscopic examination, the tumor was composed of monotonous ovoid cells with eosinophilic granular cytoplasm of moderate amount and round to oval nuclei with mild pleomorphism and prominent nucleoli. The cells were arranged in solid nests and sheets in most parts, and intervening stroma varied from thin fibrous septa to broader collagenous tissue (Fig. 1). In some areas, the tumor cells showed acinar arrangement or glandular formation with eosinophilic secretory material (Fig. 2). Areas of central necrosis were microscopically observed, comprising about 10 % of the tumor. On Periodic acid-Schiff (PAS) stain with or without digestion, PAS-positive diastase-resistant cytoplasmic granules were present in areas (Fig. 3). Immunohistochemical staining was performed by the conventional ABC method using formalin-fixed paraffin-embedded tissue sections with antibodies for pancreatic exocrine and endocrine substances (Table 1). The tumor cells were diffusely immunoreactive for amylase (Fig.3), chromogranin, neuron-specific enolase (NSE), glucagon, somatostatin and gastrin (Fig. 4), and negative for insulin and pancreatic polypeptide (PP). The staining intensity for chromogranin and glucagon slightly varied within the tumor, while other antibodies produced diffuse homogeneous stainability. Most of the cells showed both exocrine and endocrine phenotype simultaneously. None of twenty-eight regional lymph nodes showed metastatic foci.

**Fig. 1.** Solid nests of mildly pleomorphic round to oval cells, surrounded and septated by fibrovascular tissue.

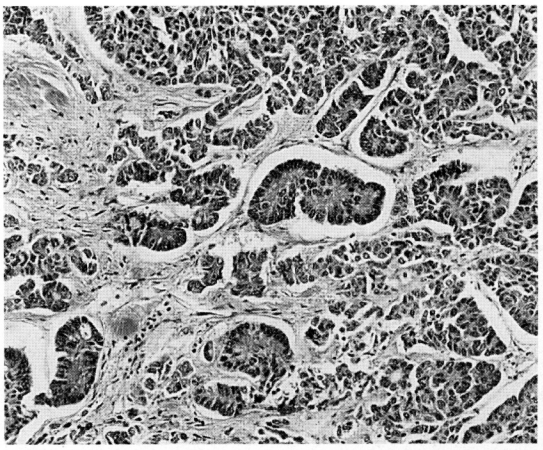

**Fig. 2.** Acinar and focally glandular differentiation of tumor cells.

**Table 1.** Antibodies used in this study

| Antigen | Antiserum | Working dilution | Source |
|---|---|---|---|
| Amylase | *P(sheep anti-human) | 1 : 100 | Biodesign |
| Chromogranin | M(mouse anti-human) | 1 : 100 | Dako |
| Neuron-specific enolase | M(mouse anti-human) | 1 : 100 | Dako |
| Insulin | P(guinea pig anti-swine) | 1 : 100 | Dako |
| Glucagon | P(rabbit anti-swine) | 1 : 100 | Dako |
| Somatostatin | P(rabbit anti-human) | 1 : 100 | Dako |
| Pancreatic polypeptide | P(rabbit anti-human) | 1 : 100 | Dako |
| Gastrin | P(rabbit anti-human) | 1 : 100 | Dako |

*P : polyclonal M : monoclonal,

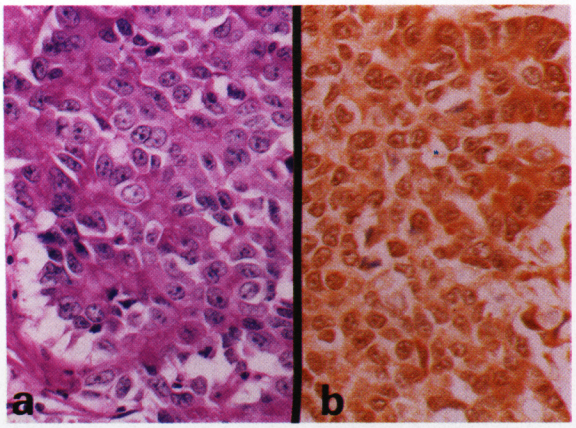


Fig. 3. Acinar features. a. PAS-positive diastase-resistant granular cytoplasm ; b. Immunohistochemical reactivity for amylase.

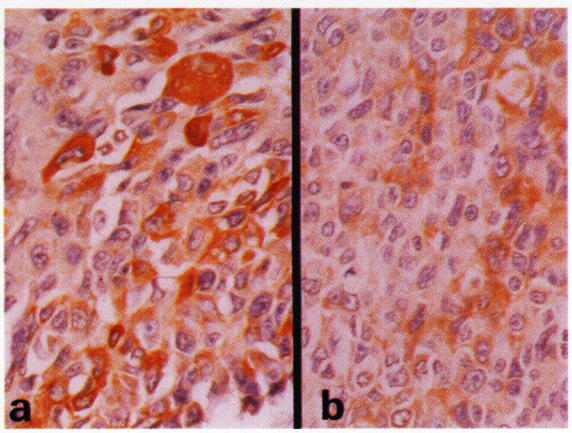


Fig. 4. Positive immunostaining for endocrine markers. a. chromogranin ; b. glucagon.

## DISCUSSION

Endocrine differentiation of carcinomas of digestive and respiratory tract is not an uncommon phenomenon. It is now believed that the APUD cells of digestive and respiratory tract are embryologically of endodermal origin (Sidhu, 1979). Thus, occurrence of endocrine cells in gastrointestinal epithelial neoplasms is not very surprising, if the neoplasms are derived from multipotent stem cells.

The pancreatic islets are also of endodermal origin, and develop in the 3rd month of fetal life from the primitive pancreatic ductules, which subsequently give rise to acinar cells. For decades, there have been constant reports on the presence of argyrophil cells in exocrine pancreatic carcinomas (Compagno and Oertel, 1979 ; Suda and Hashimoto, 1979 ; Eusebi et al., 1981 ; Kodama and Mori, 1983). Later studies using the immunohistochemical technique revealed frequent occurrence of endocrine marker-positive cells (41-100 %) in pancreatic ductal adenocarcinomas (Eusebi et al., 1981 ; Reid et al., 1982 ; Kay et al., 1985 ; Kim et al., 1990 ; Pour et al., 1993). Systemic endocrine manifestations were rarely described (Ordóñez et al., 1988), but various kinds of pancreatic hormones, most often insulin, glucagon and somatostatin have been immunohistochemically detected in these tumors (Eusebi et al., 1981 ; Reid et al., 1982 ; Kay et al., 1985 ; Pour et al., 1993). The endocrine cells in ductal adenocarcinomas were most often located at the base of neoplastic glands, or intermingled between neoplastic epithelial cells with triangular, elongated or irregular shapes (Eusebi et al., 1981 ; Kay et al., 1985 ; Pour et al., 1993). Kodama and Mori (1983) observed that the location and shape of argyrophil cells varied according to histologic type of adenocarcinomas. A better prognosis of cases containing many endocrine cells was suggested in a recent study (Pour et al., 1993).

There have been a few reports on the endocrine features of acinar cell carcinoma of the pancreas until recently (Ulich et al., 1982 ; Chejfec et al., 1985 ; Ichijima et al., 1985 ; Wiedenmann et al., 1991), probably due to the rarity of acinar cell carcinoma. Recent immunohistochemical and electron microscopic studies on acinar cell carcinomas revealed that more than one third of the cases were positive for endocrine markers (Klimstra et al., 1992 ; Hoorens et al., 1993). Klimstra et al. (1994) later collected five tumors in which the endocrine components constituted more than 25 % of the neoplasm, and designated them as mixed acinar-endocrine carcinomas (MAEC) of the pancreas. In contrast to mixed ductal-endocrine carcinomas which harbor two distinct populations, four of 5 cases of MAEC showed uniform cell populations with divergent differentiation. Most of the previously reported acinar-endocrine neoplasms in the literature were of amphicrine type as well, being composed of intermediate cells coexpressing acinar and endocrine phenotype, rather than of two populations. The tumor cells were ultrastructurally shown to have both zymogen and neurosecretory granules and /or intermediate type granules (Ulich et al., 1982 ;

Chejfec et al., 1985 ; Ichijima et al., 1985 ; Wiedenmann et al., 1991 ; Klimstra et al., 1994), and immunoreactive to acinar and endocrine markers simultaneously (Hoorens et al., 1993 ; Klimstra et al., 1994). Hence the term mixed acinar-endocrine carcinoma may not properly implicate the amphicrine nature of this neoplasm. The present case also showed single microscopic type of tumor cells of amphicrine nature with simultaneous immunoreactivity to amylase, glucagon, somatostatin and gastrin. Electron microscopic study was not performed.

On light microscopy, acinar cell carcinoma and islet cell tumor of the pancreas share a certain morphologic feature. They both can show solid, trabecular or acinar growth of rather monotonous cells with relatively abundant eosinophilic cytoplasm. Existence of mixed acinar-endocrine carcinoma may add difficulties to differential diagnosis between acinar cell carcinoma and islet cell tumors. Electron microscopy may not be always helpful, since there may be a wide size range (125-1000 nm) of zymogen granules in neoplastic acinar cells, overlapping with the size range of endocrine granules (100-450 nm) (Klimstra et al., 1992). In addition to the size problem, the same authors observed non-specific or indeterminate shape of the granules in some tumors, emphasizing the difficulty of determining the granule type by ultrastructural morphology alone.

During the embryogenesis of the pancreas, endocrine cells are closely related with acinar cells, and certain forms of intermediate cells have been identified in the normal pancreas of various vertebrate animals including humans (Melmed, 1979). In animal experiment, Pour and Bell (1989) found proliferation of amphicrine cells producing both mucin and endocrine substances during pancreatic carcinogenesis in the hamster model. Human pancreatic carcinomas of amphicrine mucious-endocrine type have also been reported (Kniffin et al., 1988 ; Ordóñez et al., 1988). The histogenesis of mixed exocrine-endocrine or amphicrine type carcinomas of the pancreas could be explained by derivation of neoplasm from these normally occurring intermediate cells or primitive multipotent cells that have the capacity to differentiate in several directions, or by dedifferentiation of neoplasia into embryonic stage which could give rise to acinar, endocrine, and ductal cells (Jamieson et al., 1981). There is a case report of pancreatic carcinoma with duct, endocrine, and acinar differentiation (Schron and Mendelsohn, 1984).

The biologic aggressiveness of MAEC is as yet uncertain because of a small number of cases. Klimstra et al. (1994) assumed the behavior of MAEC to be similar to that of acinar cell carcinoma. More to the clinical aspect, it is noteworthy that not a small number of pancreatic neoplasms show both exocrine and endocrine phenotype, reflecting the close histogenetic relationship between the two components of this organ. Continuous immunohistochemical study on pancreatic exocrine neoplasms would be of value in discovering more cases.

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