Pancreatic Endocrine Tumor Admixed with a Diffuse Microcystic Adenoma - A Case Report -

We report a case of pancreatic endocrine tumor admixed with a diffuse microcystic adenoma in a 67-year-old woman with a six months history of melena. Whipple's operation and near-total pancreatectomy were performed under the impression of a pancreatic cancer with duodenal invasion. The pancreas was enlarged and was entirely replaced by sponge-like tiny cysts, which were lined by a single layer of periodic acid Schiff positive cuboidal cells. Also encountered was a gray white solid area at the head portion which extended to the duodenum with an intraluminal polyp formation. The compact area was composed of solid and acinar structures of tumor cells, which showed a positive reaction for chromogranin A and neuron specific enolase, separated by delicate highly vascularized stroma. To the best of our knowledge, this is the first case report published with immunohistochemical studies to deal with a pancreatic endocrine tumor admixed with a diffuse microcystic adenoma.
(JKMS 1997; 12: 469~72)

Key Words : *Pancreatic endocrine tumor; Microcystic adenoma; Pancreas*

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Received : May 15, 1997
Accepted : June 7, 1997

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INTRODUCTION

Microcystic adenoma, also known as glycogen-rich or serous cystadenoma represents 1 to 2% of pancreatic neoplasms. The risk of malignant behavior is almost negligible. Patients are usually elderly, and there is no sex predilection (1). These lesions may be asymptomatic or produce abdominal mass or pain. Most cases are solitary, and quite bulky at discovery, generally occurring in the pancreatic head, but a few multicentric examples have been reported (2). Some of the cases occur in the context of von Hippel-Lindau disease (3) and a few reported cases have coexisted with pancreatic ductal carcinoma (4, 5). Until the present, two cases of microcystic adenoma coexistent with pancreatic endocrine tumors (3, 6) and only one case of a pancreatic endocrine tumor arising within a microcystic adenoma have been reported (7). We experienced a pancreatic endocrine tumor admixed with a diffuse microcystic adenoma of which we undertook pathological and immunohistochemical studies to better elucidate the nature of this lesion.

CASE REPORT

A 67-year-old woman presented with intermittent melena which had persisted for 6 months. She had had a history of cholecystectomy for gallbladder stones and diabetes mellitus for 6 years. All of the laboratory data were within normal limits, except for a high blood glucose level (245 mg/dl). Endoscopic retrograde choledochopancreatographic (ERCP) examination revealed a 3 cm sized polypoid mass with surface ulceration and bloody oozing at the duodenal second portion. An abdominal computed tomography (CT) scan showed an enlarged pancreas which was near totally replaced by varying sized cysts with multifocal calcifications. In the head of the pancreas a well enhanced mass with high attenuation was found and this mass invaded to the duodenum (Fig. 1). Under the impression of pancreatic cancer with duodenal invasion, Whipple's operation and a near total pancreatectomy was performed.

The resected pancreas measured $16 \times 6 \times 7$ cm in size and showed an irregular bosselated contour with peripheral calcification. On section, the pancreas was replaced by numerous gray white sponge-like tiny cysts which ranged from 0.1 to 1.0 cm in diameter. Most of the cyst wall was paper thin, but thick fibrous wall was also encountered in the multifocal area (Fig. 2). The cystic spaces were filled with clear serosanguinous and bloody fluids. Also noted was an ill-defined brownish solid tumor mass at the head portion measuring 2.8×1.3 cm in cross

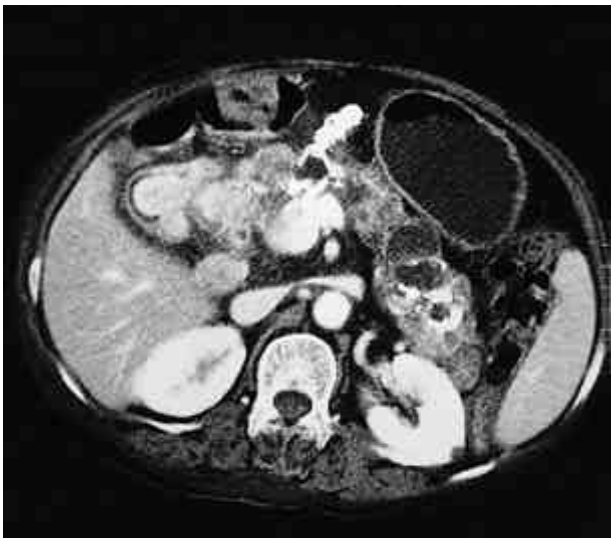

Fig. 1. Abdominal computed tomography (CT) scan reveals numerous varying sized cysts throughout pancreas and a well enhanced mass in the head, which invades to the duodenum.

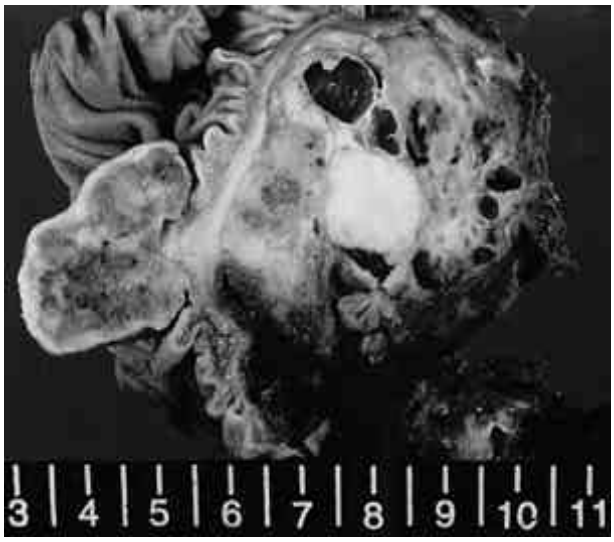

Fig. 3. The solid tumor invades the duodenum with polypoid growth.

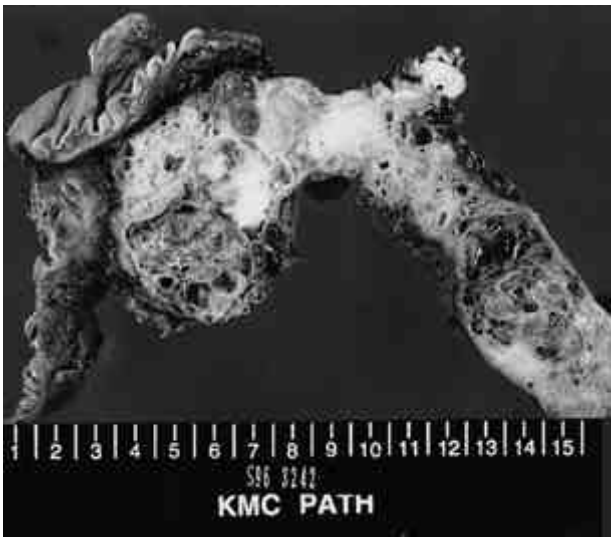

Fig. 2. The pancreas is diffusely replaced by cystic tumors with a single, nonencapsulated solid tumor.

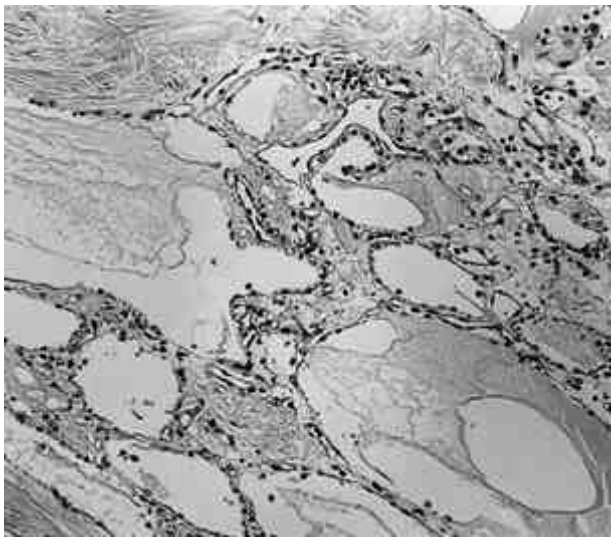

Fig. 4. The cysts are lined by cuboidal and flatttened cells with surrounding fibrous wall.

diameter, which invaded to the duodenum. On the duodenal surface there was a gray white intraluminal polypoid mass showing focal surface ulceration measuring 3×2.5×2 cm (Fig. 3).

Microscopically, the pancreas revealed numerous cysts of various sizes lined by a single layer of flat to cuboidal epithelial cells (Fig. 4). Rare tiny papillary growths were formed by the cuboidal cells within the cystic structures. The lining epithelial cells had uniform small round nuclei and clear to pale eosinophilic glycogen-containing cytoplasms, which were stained by periodic acid Schiff stain. Nuclear stratification and cytologic atypia were not seen. Fibrosis and calcification in the cystic walls were seen. The solid tumor was encased by the microcystic adenoma (Fig. 5). This portion consisted of acinar or tubular structures or solid tumor cell nests, separated by delicate fibrous stroma with abundant vasculature, including sinusoid-like vascular channels (Fig. 6). The tumor cells were mostly round or polygonal shapes having round nuclei with inconspicuous nucleoli and abundant pale to eosinophilic cytoplasms. Infrequently, large, sometimes irregularly shaped cells with large nuclei were found. The

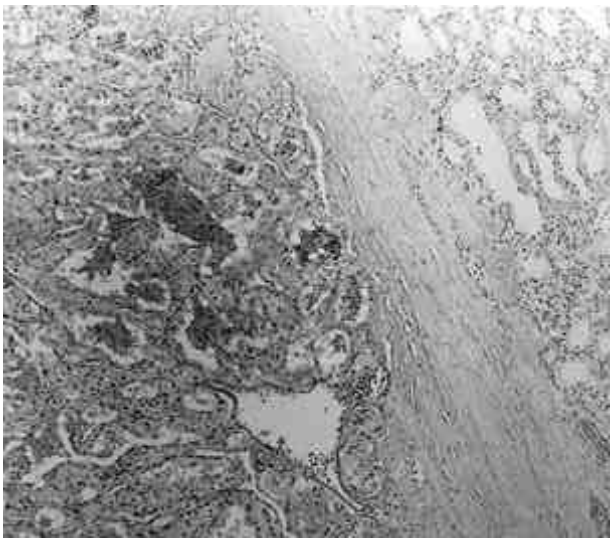

Fig. 5. The solid tumor is surrounded by variable sized cysts.

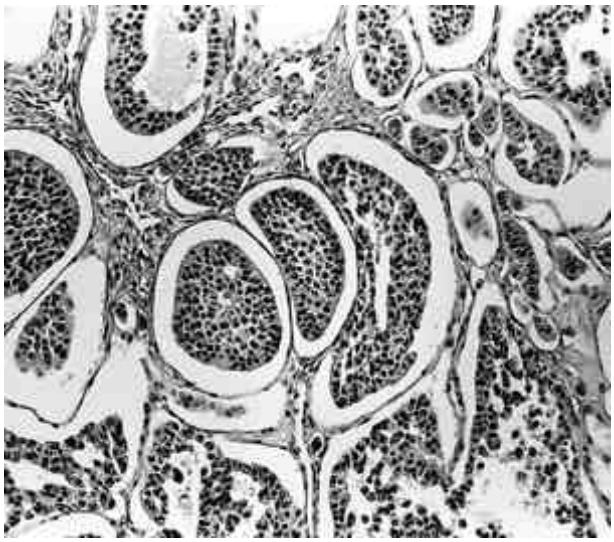

Fig. 6. The solid area consists of compact tumor cell nests, separated by delicated fibrous stroma with abundant vasculature.

solid portion of the tumor invaded the duodenal wall with frequent lymphatic emboli. Surface ulceration and underlying granulation tissue proliferation were also noted.

Immunohistochemically, the cyst lining cells showed a positive reaction to the antibodies for cytokeratin, epithelial membrane antigen, but were negative for neuron specific enolase and chromogranin A. The cytoplasms of tumor cells in the solid portion were diffusely and strongly stained by antibodies for neuron specific enolase and chromogranin A, but not for all pancreatic neuroendocrine products, including insulin, glucagon, vasoactive intestinal polypeptide, gastrin, substance P, somatostatin, and pancreatic polypeptide.

DISCUSSION

In this report, we describe a pancreatic endocrine tumor admixed with a microcystic adenoma. Two cases of a pancreatic endocrine tumor with a separate microcystic adenoma have recently been described (3, 6). The specific coincidence of these two entities in the same mass has been reported only by Keel et al. (7), who described a 7.5 cm microcystic adenoma admixed with a 1.5 cm sized nonfunctioning pancreatic endocrine tumor in a 47-year-old woman. Our case showed characteristically diffuse involvement of the microcystic adenoma in the pancreas admixed with a nonfunctioning pancreatic endocrine tumor which invaded the duodenum with frequent lymphatic emboli. Definite regional lymph nodes and liver metastasis were not found. Diffuse involvement of microcystic adenoma is very rare. Of the 34 cases of microcystic adenomas described by Compagno and Oertel (8), three involved the entire pancreatic tissue. The photographs from one of them appeared to illustrate two or more nodular masses with different growing centers. Kim et al. (2) described the histogenesis of the multicentric development of microcystic adenomas as multifocal tumor growths from the progenitor cells and suggested that one of Compagno and Oertel's cases with entire pancreatic involvement may have resulted from the confluence of two or more separately developed neighboring microcystic adenomas. We think our case was probably multifocally originated and that later these cystic lesions were increased and conglomerated, so finally they totally replaced the entire pancreas. All pancreatic endocrine tumors should be regarded as potentially malignant, usually their behavior cannot be predicted from their histopathological features or their specific cellular products. Features that correlated with a greater metastatic potential are definite stromal invasion, tumor emboli in pancreatic vessels, and a glandular or solid rather than gyriform pattern of growth (9). Our case showed duodenal invasion with lymphatic emboli, so we think that this case had malignant potential but definite distant metastasis was not seen.

The histogenesis of these admixed tumors is not clear, but between the two hypotheses; (a) coincidental neoplastic change in two different cell types and (b) neoplastic change of a single common precursor cell, the latter is more compatible with the intricate admixture of the different cell types and patterns (10). In the light of the common histogenesis of the endocrine and exocrine pancreas, which both develop from the endodermal lining of the duodenum, the potential of pancreatic ductal stem

cells for biphasic differentiation along either glandular epithelial or neuroendocrine pathways would not be unexpected. Indeed, biphasic differentiation is observed in many different pancreatic disorders, such as nesidioblastosis, amphicrine carcinoma, and mixed acinar-endocrine carcinoma (7). Nesidioblastosis is the prototypic non-neoplastic disorder in which coincident epithelial and endocrine differentiation occurs. These lesions are believed to represent neuroendocrine differentiation of epithelial stem cells within the pancreatic ducts (11). Ductal epithelial tumors with the potential for biphasic differentiation are also known to occur. Amphicrine carcinomas produce tumors showing a combination of pancreatic endocrine tumor-like features and features of either ductal or acinar cell differentiation within the same cells. The cells of amphicrine neoplasms show evidence of simultaneous neuroendocrine granule formation and mucin production within a single neoplastic cell (12). Another pattern of mixed differentiation is manifested by the concurrent development of distinct epithelial and neuroendocrine cells within the same tumor. Such tumors include mixed acinar-endocrine carcinoma of the pancreas, a recently defined malignancy in which endocrine cells constitute more than 25% of an otherwise acinar neoplasm (13). In our case, the tumor was composed of serous epithelial and neuroendocrine components. We think that our case is another example of the potential for biphasic differentiation in pancreatic duct epithelial neoplasia.

In our case, differential diagnosis from acinar cell cystadenocarcinoma seems to be difficult. Acinar cell cystadenocarcinoma is composed of cysts and tubules of varying size. Some of them are small and densely packed cysts with transition to a solid portion. The cyst is lined by tall cylindric cells with basement membrane and cuboidal to flattened cells. The characteristic feature of this neoplasm is papillary growth of the malignant cells into the cystic spaces. Immunohistochemically, the tumor cells show positive reaction to the zymogen granules. In contrast to our case the results of the immunohistochemical studies for chromogranin A and neuron specific enolases are negative (14).

Our case emphasizes the importance of adequate gross examination and sampling of grossly apparent microcystic adenoma which might draw attention away from another synchronous pancreatic neoplasm. Liberal sampling of fibrotic or solid areas of the noncystic native pancreatic parenchyma should be performed in cases of benign pancreatic neoplasia.

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