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Cytology of malignant endocrine tumor of the pancreas : A case report

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ABSTRACT

We report here a case of malignant endocrine tumor of the pancreas with lymph node metastasis in a 67-year-old woman. The cytologic preparations exhibited small cells having uniform round eccentrically located nuclei and large cells showing irregular-shaped nuclei with coarse chromatin and pleomorphism. The histologic, immunohistochemical and ultrastructural findings were characteristic of pancreatic endocrine tumor, regardless of immunophenotypic heterogeneity. The heterogeneity observed in cytologic specimens may be important in predicting the malignant potential of this tumor group.

Key words : Cytology, Malignant neoplasm, Pancreatic endocrine tumor, Immunohistochemistry

INTRODUCTION

The diagnosis of endocine tumor of the pancreas can be suspected on cytologic examination, including fine needle aspiration biopsy (1-3). Although this examination may provide useful information about the tumor to clinicians, the biological behavior of the tumor is not predicted solely by the cytological findings (2). We report a case of malignant endocrine tumor of the pancreas whose cytologic features are considered to be the reflection of malignant potential.

CASE REPORT

A 67-year-old Japanese woman with a 10 year history of diabetes mellitus complained of an upper abdominal discomfort. Computed tomography of the

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abdomen revealed the presence of a mass located in the pancreas head (Fig. 1). The well-circumscribed mass measuring 4 cm in maximum diameter showed little enhanced effects. Serum measurements of insulin, somatostatin, glucagon and gastrin were within normal ranges, and there was no clinical evidence of a distinct hormonal syndrome or multiple endocrine neoplasia. The patient then underwent a total pancreato-duodenectomy with lymph node resection under the diagnosis of a malignant tumor.

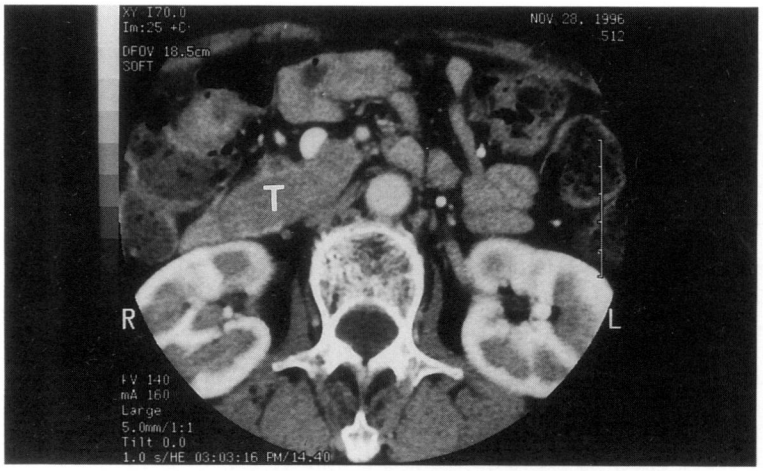

Fig. 1 Computed tomography scan showing a mass located in the pancreatic head (T).

Macroscopically, the resected tumor originating in the pancreas head did not have a well-defined capsule, and was pinkish and multinodular, extending into the lumen of the pancreatic duct. Imprint smears were directly obtained from the exposed tumor. The smears were immediately wet fixed in 95% ethanol and stained by the Papanicolaou method. The resected specimen was fixed in 10% formalin and embedded in paraffin. Sections were routinely stained with hematoxylin-eosin. Immunohistochemical studies were carried out on the ethanol-fixed imprinted specimens and formalin-fixed, parafin-embedded tissues according to the streptoavidin-biotin complex method.

CYTOLOGICAL FINDINGS

The touch smears showed numerous polygonal cells in isolated and loose aggregates in a background that contained a few red blood cells and mononuclear inflammatory cells. Two types of tumor cells were recognized : One was cells having uniformly round eccentrically located nuclei. The cytoplasm was moderate in amount and fine granular (Fig. 2A). The other is the cells showing

irregular-shaped nuclei with coarse chromatin and pleomorphism. They had abundant amounts of basophilic cytoplasm and formed small clusters and cord-like aggregates (Fig. 2B). A morphological transition between them was also observed. The cytologic preparation was diagnosed as a pancreatic endocrine tumor. Immunohistochemical stainings revealed that both types of tumor cells were positive for chromogranin A and wide-spectrum keratin (deta not shown).

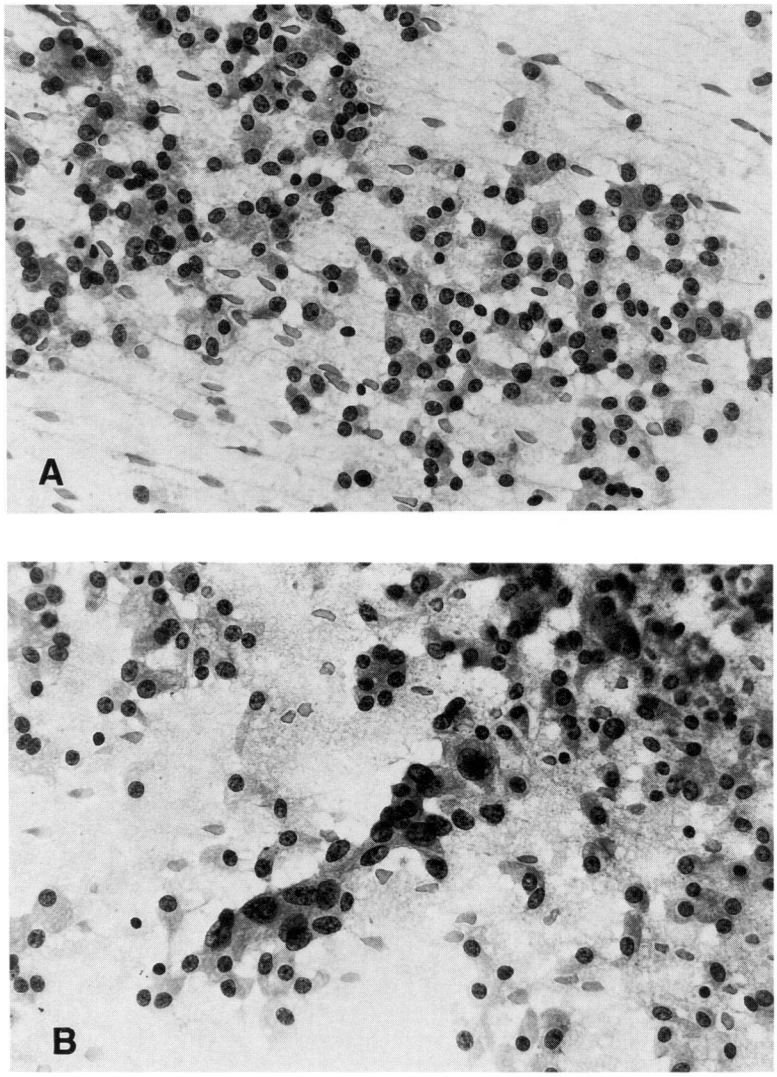

Fig. 2 (A) Uniformly small tumor cells having round eccentrically located nuclei present singly or in small clusters (Papanicolaou stain ; X 400). (B) Large cells showing irregular-shaped nuclei with pleomorphism form cord-like aggregates in the background of small tumor cells (Papanicolaou stain ; X 400).

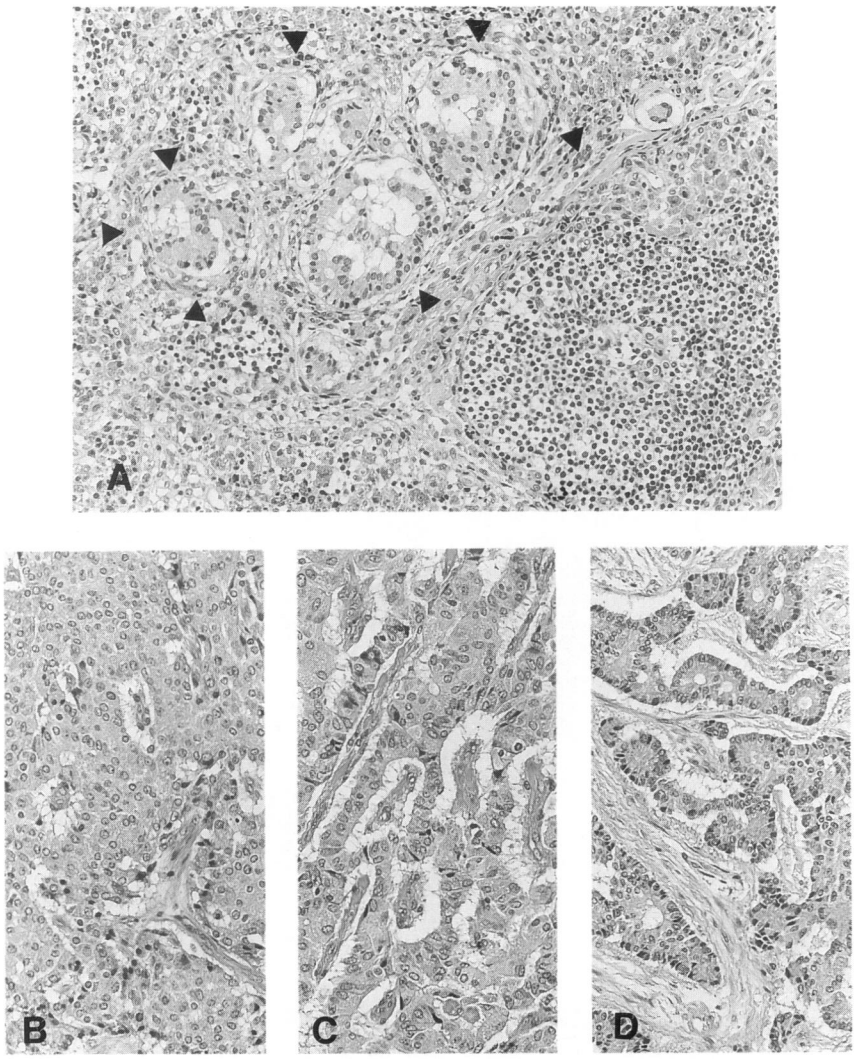

Fig. 3 Histologic sections of a lymph node containing metastatic tumor (A) and primary pancreatic tumor (B-D) (hematoxylin and eosin ; X 200). Tumor cells showing (B) solid, (C) gyriform and (D) glandular patterns.

HISTOLOGIC, IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL FINDINGS

The tumor proliferated in a multinodular fashion with invasion into the pancreatic duct and metastasis to a regional lymph node (Fig 3A, 4). In hematoxylin-eosin staining, the microscopic appearance of primary tumor was typical for pancreatic endocrine tumor. The tumor was composed of cuboidal

cells with centrally located nuclei and acidophilic or amphophilic, finely granular cytoplasm. The pattern of growth was varied according to the tumor nests, and included solid, gyriform, or glandular patterns (Fig 3B-D). The tumor cells diffusely showed immunohistochemical reactivity for chromogranin A. Some tumor cells expressed focal positivity for wide-spectrum keratin, cytokeratin 19 (CK19) and CA19-9. Immunohistochemical staining with MIB-1, a monoclonal antibody to Ki-67 antigen, revealed that the tumor contained "active areas" showing high MIB-1 index (>10%) (Fig 4). Stains for cytokeratin 20, serotonin, insulin, glucagon, somatostatin and ACTH were negative in all tumor cells. Ultrastructurally, the tumor cells contained electron-dense, round, membrane-bound secretory granules that measured 200 to 300nm in diameter (Fig 5). Zymogen granules were not detected.

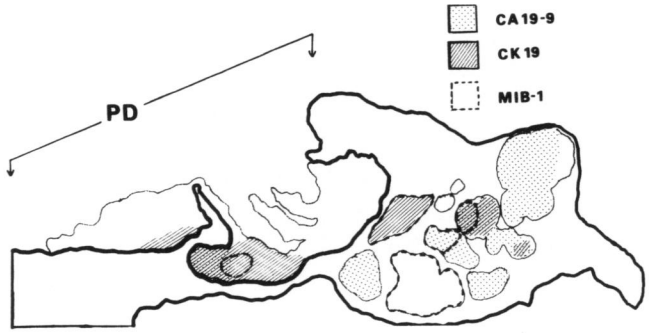

Fig. 4 Schematic illustration showing the distribution of tumor cells positive for CA 19-9 or CK 19. Dotted square representing high MIB-1 index areas (>10%). Note that all tumor cells are positive for chromogranin A. (PD ; pancreatic duct)

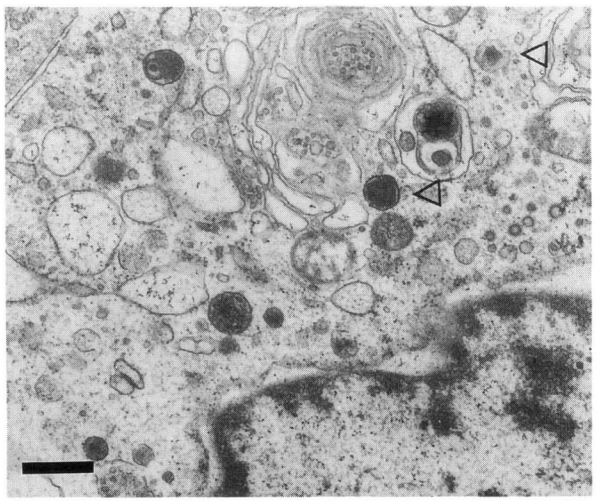

Fig. 5 Ultrastructural picture showing round membrane-bound secretory granules that contain crystalline cores (open triangle) (bar = 500nm).

DISCUSSION

It has been believed that the biologic behavior of pancreatic endocrine tumors cannot be predicted from the histologic or cytologic features as seen in routinely stained sections (4-7). The majority of them are generally slow-growing neoplasms, the inconspicuous evidence of malignancy is angioinvasion, gross infiltration of adjacent organs, or metastasis. Nuclear pleomorphism and mitotic activity are unreliable for distinguishing benign from malignant tumors. Recent immunohistochemical studies suggested that several markers had diagnostic value. Human chorionic gonadotropin and its alpha and beta subunits have been proposed as markers of malignancy in pancreatic endocrine tumors (8). The expression of progesterone receptors correlated with an absence of metastases and lack of invasion into neighboring organs (9). The cell cycle-related antigen, proliferating cell nuclear antigen or Ki-67, may predict malignant behavior (10).

It has been reported that the expression of both neuroendocrine and ductular phenotypes may serve as a marker for malignancy of pancreatic endocrine tumors (11, 12). This dual differentiation in tumor cells was also observed in the present case. Immunohistochemical stainings revealed that chromogranin A, a neuroendocrine marker, was diffusely positive, and ductular markers, wide-spectrum keratin, CK 19, CA 19-9 and CEA were heterogeneously positive in the tumor cells (Fig. 4). The immunohistologic heterogeneity of this tumor may reflect the process of tumor progression (13). These findings also support the idea that the precursors of these tumors are presumably multipotent in terms of their capacity to differentiate into various cell types, including the ductular epithelium (4, 14).

Although it is difficult to make the diagnosis of a "malignant" endocrine tumor of the pancreas solely by cytologic evaluation (2), Tao has recently proposed the cytologic criteria of malignancy, including nuclear size, cell size, multinucleated tumor cells, mitotic figures and necrotic tumor debris (3). These cytologic findings may reflect phenotypic heterogeneity. In the present case, the presence of pleomorphism in nuclear and cell size, and immunocytochemical positivity for both chromogranin A and wide-spectrum keratin were detected in imprinted specimens. Consideration of phenotypic heterogeneity thus may play a significant role in assessing biologic behavior of pancreatic endocrine tumors.

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