

A Case of Benign Intraductal Papillary Mucinous Neoplasm of the Pancreas Containing Two Major Subtypes

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Abstract

Here we report a case of benign intraductal papillary-mucinous neoplasm (IPMN) of the pancreas containing two major subtypes. A 73-year-old man underwent pancreatoduodenectomy for a cystic mass, 5.0 cm in diameter. Histopathologic examinations revealed that IPMN was composed of gastric-type adenoma and intestinal-type borderline lesion. Marked intraluminal nodular growth was observed in the center of the tumor composed of intestinal-type cells positive for MUC2. Our observations suggest that gastric-type epithelium is a precursor of intestinal-type lesions in the stepwise progression of IPMN.

Keywords

Intraductal papillary mucinous neoplasm (IPMN) – MUC2 – subtype.

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is classified into four subtypes: gastric, intestinal, pancreatobiliary and oncocytic, on the basis of histological features and mucin expression comprising MUC1, MUC2, and MUC5AC [1]. The two major subtypes are gastric and intestinal types. Detailed clinicopathologic analyses and comparison of each subtype have revealed that gastric-type IPMN has lower malignant potential than intestinal-type IPMN. Recent reports of a case series of resected IPMN specimens classified the neoplasms as a single subtype [2, 3]. Combined phenotypic features consisting of gastric- and intestinal-IPMN have rarely been reported, and therefore the histogenesis of and the relationship between subtypes are

unclear. In the present case, IPMN involving both the main pancreatic duct and smaller branch ducts was composed of gastric-type adenoma and intestinal-type borderline lesions. Detailed assessment of the distribution of each phenotype suggests that gastric-type epithelium is a precursor of intestinal-type lesions.

Case report

A 73-year-old man was referred to our hospital with slight nausea and weight loss in September 2006. The serum level of carbohydrate antigen 19-9 (CA 19-9) was elevated - 95.5 U/ml (normal range: 0-37 U/ml). Computed tomography (CT) revealed a round cystic mass of 5.0cm in diameter with solid component in the pancreas head (Fig. 1A). There was no diffuse dilation of the main pancreatic duct throughout the pancreas body or tail. The peripheral area of the mass showed similar density to that of the pancreatic parenchyma, suggesting that this mass might be a cystic dilation of the main pancreatic duct. Endoscopic retrograde pancreatography showed marked dilation of the main pancreatic duct limited to the pancreas head with round filling defect (Fig. 1B). The downstream duct was slightly dilated but showed no irregularity. On the basis of these findings, a main duct-type IPMN was suspected. The solid component shown by CT and the elevated serum CA19-9 level suggested malignancy. Therefore, a pancreatoduodenectomy was performed in October 2006.

The excised specimen was fixed in formalin, and the entire pancreas head was studied in step-by-step sections. Each block was embedded in paraffin and cut, and sections were stained with hematoxylin and eosin or for immunohistochemistry (IHC). IHC for MUC2 was carried out with a monoclonal antibody (1: 150, Novocastra Laboratories, Newcastle upon Tyne, UK). Grossly, the resected lesion consisted of a markedly dilated pancreatic duct filled with mucin and a thickened ductal epithelium including intraluminal nodular projections. The gross appearance, representative sections, and histologic features are shown in Fig. 1C. Near the cut end of the pancreas, branch ducts formed a low-grade pancreatic intraepithelial

Received: 27.09.2007 Accepted: 20.11.2007

J Gastrointest Liver Dis

December 2008 Vol.17 No 4, 457-460

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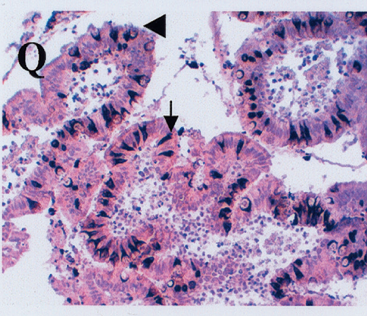
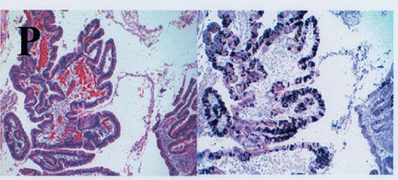
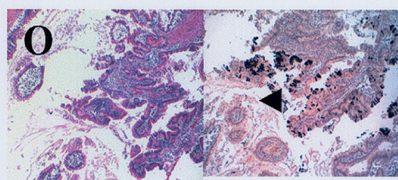
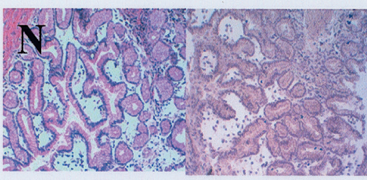
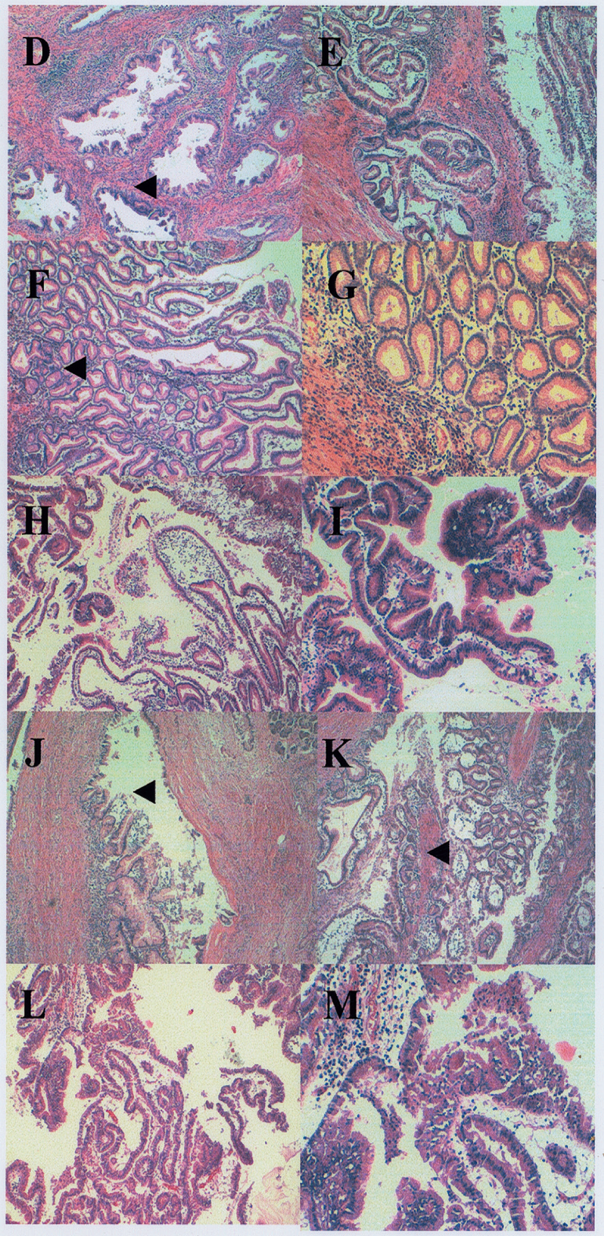
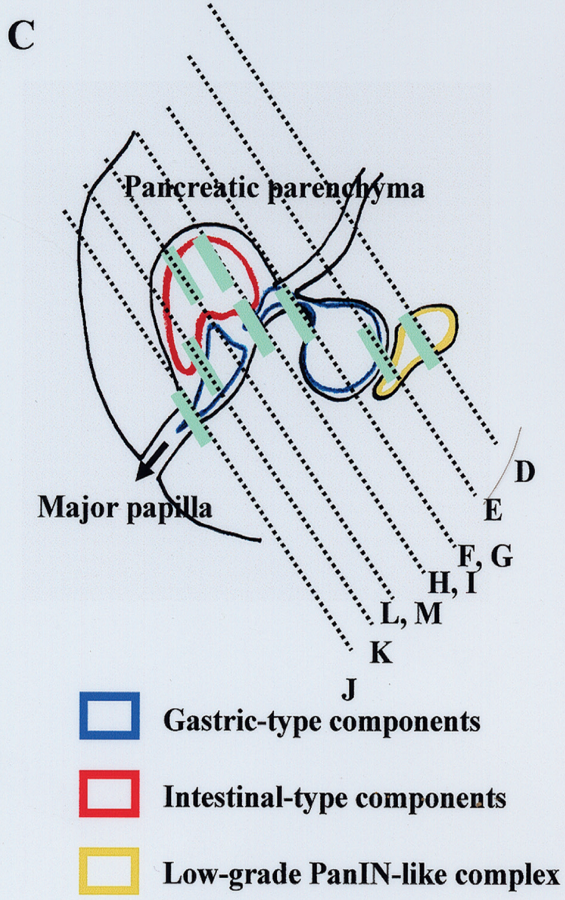
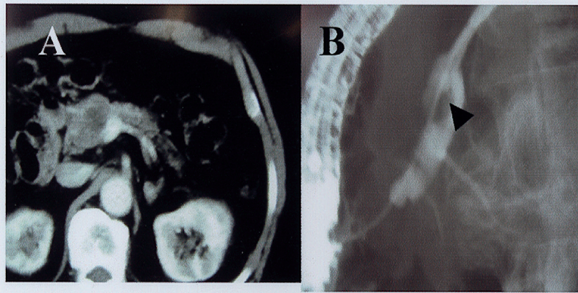
Fig 1. (opposite page) (A) Computed tomography scan shows a large (4.0cm in diameter) complex cystic mass in the head of the pancreas. The peripheral area of the mass is slightly enhanced in the portal phase. Irregular solid components are visible in the mass (arrowhead). Dilation of the main pancreatic duct in the pancreas body and tail is not observed. (B) Endoscopic retrograde pancreatogram shows dilation of the main pancreatic duct limited to the pancreas head with irregular filling defect (arrowhead). The downstream duct is smooth and slightly dilated. (C) Schema showing the gross appearance, histologic features, and representative sections of the pancreatic head obtained by pancreatoduodenectomy. (D) Adjacent to the cut end of the pancreas, branch ducts form a low-grade PanIN-like complex. Flat to micropapillary lesions composed of tall columnar cells with basally oriented nuclei are considered PanIN-1A. Some ducts show papillary and pseudostratified structures corresponding to PanIN-1B (arrowhead) (original magnification, X40). (E) Marked papillary growth without atypia is observed communicating with the low-grade PanIN-like complex. Papillary structures are simple and composed of tall columnar cells with basally oriented nuclei and clear eosinophilic cytoplasm, comprising gastric-type IPMN adenoma (X40). (F) Gastric-type adenoma extends continuously into the main pancreatic duct. The basal area of the papillary epithelium is composed of clear packed glands with intervening narrow stroma, representing pyloric gland-like structures (arrowhead) (X40). (G) High-magnification images of gastric-type adenoma. Nuclei are basally located, and no dysplasia is visible. A flat epithelium is observed in part (X200). (H) At the center of the tumor in the main pancreatic duct, gastric-type adenoma is replaced by cells with dark eosinophilic cytoplasm and oval- to spindle- shaped nuclei, forming irregular papillary structures, comprising intestinal-type IPMN (X40). (I) High-magnification images of the intestinal-type IPMN. Pseudostratified structures are visible (X200). (J) In the main pancreatic duct adjacent to the major papilla, the normal epithelium is gradually replaced by gastric-type epithelium (arrowhead) (X40). (K) The gastric-type adenoma extends distally replacing the epithelium of the main duct, and changes to the intestinal type at the center of the tumor (arrowhead) (X200). (L) The intestinal type shows marked intraductal nodular growth (X100). (M) Intestinal type includes cells with loss of polarity and nuclear crowding, corresponding to an IPMN borderline lesions (X200). (N-P) Representative images of immunohistochemical analysis for MUC2. Hematoxylin and eosin staining is shown in the left column, and corresponding immunohistochemical staining is shown in the right column. (N) Gastric-type components are negative for MUC2 staining. (O) At the boundary between gastric- and intestinal-type components, intestinal-type components are positive for MUC2 staining (arrowhead). (P) Intestinal-type components showing intraductal nodular growth show diffuse MUC2 staining. (Q) MUC2 staining is localized mainly in the cytoplasm (arrow) and in part around nuclei (arrowhead).

neoplasia (PanIN)-complex (Fig. 1D). IPMN components were observed communicating with the PanIN complex (Fig. 1E), as were clear eosinophilic neoplastic epithelial cells with round, basally oriented nuclei (Fig. 1F, G). Pyloric gland-like structures were present in the basal area of the epithelium. Tumor cells showed no dysplasia. These components together were considered to comprise gastric-type adenoma. IPMN components showing gastric-type morphology extended continuously to the main pancreatic duct. In the center of the tumor, transition from a gastric phenotype to another phenotype was observed (Fig. 1H). In the main pancreatic duct proximal to this transition site, dark eosinophilic cells with pseudostratified spindle-shaped nuclei formed a papillary configuration (Fig. 1I), considered to comprise an intestinal-type borderline lesion. In the main pancreatic duct adjacent to the major papilla, the epithelium of the normal main duct was gradually replaced by gastric-type adenoma (Fig. 1J) changing to an intestinal phenotype in the center of the tumor (Fig. 1K). At the center of the tumor, tumor cells showed marked intraluminal nodular growth (Fig. 1L), and some cells showed an irregular papillary configuration and loss of polarity (Fig. 1M). IHC analysis revealed that tumor cells with gastric-type morphology were negative for MUC2 staining (Fig. 1N). Intestinal-type components showed diffuse MUC2 staining (Fig. 1O, P), consistent with previous reports [4]. The boundary of each phenotype was clearly visualized by MUC2 immunohistochemistry (Fig. 1O, arrow). MUC2 staining was observed mainly in the cytoplasm (Fig. 1Q, arrow) and in part around the nuclei (Fig. 1Q, arrowhead). On the basis of these observations, combined-type IPMN containing two major phenotypes (gastric and intestinal) was diagnosed.

Discussion

In the present case, preoperative radiographic findings suggested IPMN with malignancy on the basis of marked dilation of the main pancreatic duct with a filling defect, and apparent solid components in the cystic mass as shown by CT. These findings indicated that the tumor was localized mainly in the main pancreatic duct and that it contained intraluminal nodular growths, characteristic for malignant IPMN [5-7]. The patient had a history of alcohol abuse, nausea, weight loss, and elevated serum CA19-9 level. These clinical features are considered signs of malignancy in IPMN [8]. However, histologic examination of the resected pancreas showed IPMN consisting mainly of adenoma with some borderline lesions. Carcinoma was not detected throughout the tumor. The discrepancy between radiologic and histologic findings in the present case may be due to the phenotypic features of the tumor.

The gastric type and intestinal type are the two major subtypes of IPMN [1]. Recent reports have revealed that gastric-type IPMN usually presents in peripheral branch ducts with low-grade atypia, corresponding to IPMN adenoma, and that intestinal-type IPMN usually presents as a large lesion involving the main duct with marked atypia, corresponding to intraductal papillary mucinous borderline category or intraductal papillary mucinous carcinoma [1]. Generally, gastric-type IPMN has a lower malignant potential than does intestinal-type IPMN [2]. In the present case, gastric-type IPMN was predominant in both branch ducts and the main duct, contributing to the low malignant potential of this tumor. Intestinal-type IPMN was located only in the center of the tumor and formed intraductal nodular growths.



Recent reports have evaluated the histopathologic characteristics of gastric- and intestinal-type IPMN [2]. However, the neoplasms were described as a single phenotype [2, 3]. IPMN comprising both gastric and intestinal phenotype has rarely been reported. Nakamura et al [4] reported two cases with a combined histologic appearance of gastric- and intestinal-type IPMN among 50 cases of IPMNs; only the area composed of intestinal-type IPMN cells showed MUC2 staining. The histogenesis of intermingled gastric- and intestinal-type cells is unclear. In the present case, peripheral areas of the tumor comprised gastric-type IPMN, and central areas of the tumor comprised intestinal-type IPMN. In the periphery adjacent to the cut end, gastric-type adenoma communicated with a low-grade PanIN-like complex. In addition, in the periphery near the major papilla, the normal epithelium of the main duct was gradually replaced by gastric-type IPMN cells. Change from a gastric to intestinal phenotype was observed in the main duct at the center of the tumor. These findings suggest that intestinal-type components arose from gastric-type components in this case. Furukawa et al [1] hypothesized that an area with gastric-type IPMN epithelium is a common precursor of the other types, including intestinal-type IPMN, because gastric-type IPMN usually involves the small branch ducts, and the other types involve the main duct. An association between low-grade PanIN and gastric-type IPMN has been reported [2, 9]. However, morphogenesis of gastric-type epithelium in the main duct has not been described.

In the present case, gradual (not abrupt) replacement of normal epithelial cells with gastric-type IPMN cells was observed in the main duct, suggesting that gastric-type IPMN may be a precursor of intestinal-type IPMNs in the main duct. To address this, analysis of the phenotypic distribution

of IPMN in a case series of resected IPMNs is in progress in our laboratory.

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