Clinicopathological Analysis of Growth Patterns of Malignant Intraductal Papillary Mucinous Tumors of the Pancreas
- Unusual Growth Pattern of Fistulous Extension -

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Background : Usually, a malignant intraductal papillary mucinous tumor (IPMT) of the pancreas shows invasive carcinoma. Recently, IPMT with an unusual growth pattern of a fistulous extension was reported. However, little is known about malignant IPMTs with a different growth pattern of invasion and fistulous extension. Methods : Malignant IPMTs were classified into invasive (colloid or tubular type) carcinomas and the fistulous extension type according to their growth patterns. Their clinicopathological characteristics were compared. Results : Among a total of 68 cases of IPMT, there were 16 cases with malignant IPMT: eight, six and two of the colloid, tubular, and fistulous extension types, respectively. The immunohistochemical (IHC) expression of MUC1 was found in seven out of eight colloid and five out of six tubular types, but there was no IHC expression of MUC1 in the fistulous extension type. The IHC expression of MUC2 was noted in one of the eight colloid, one of the six tubular and in both cases with the fistulous extension type. There was no difference in the tumor recurrence rates between the different growth patterns. Conclusions : IPMT with the fistulous extension type has a peculiar extension pattern consisting of multiple fistulous tracts without a mass. Although most of the epithelium in the fistulous tract show moderate to severe dysplasia, only the fistulous extension should be considered to be an unusual growth pattern of malignant IPMT. The clinical significance of this unusual type of IPMT remains to be determined.

Key Words : Intraductal papillary mucinous tumor; Pancreas; Fistulous extension

Intraductal papillary mucinous tumors (IPMT) are characterized by the intraductal proliferation of mucinous cells that are usually arranged in a papillary pattern.1-3 According to the World Health Organization (WHO) classification of tumors, IPMT is classified into a benign adenoma, a borderline malignancy with moderate dysplasia and a malignant carcinoma.1 The malignant forms of IPMT are subclassified into non-invasive and invasive carcinomas. In the latter cases, the invasive component may assume the appearance of a colloid or tubular type of carcinoma.4 Invasive IPMT commonly presents as a mass lesion. Recently, an unusual growth pattern with a fistulous extension of a malignant IPMT with or without an invasive carcinoma component was reported.6-8 However, there have been few detailed clinicopathological analysis of the different growth patterns of malignant IPMT. This study compared the clinicopathological characteristics of malignant IPMT with different growth patterns.

MATERIALS AND METHODS

All cases of IPMT between 1995 and 2005 were retrieved from the surgical pathology files at the Samsung Medical Center. The IPMT cases were classified according to the WHO classification, and those with malignant IPMTs with invasive growth or fistulous extension were selected. Malignant IPMTs with invasive growth were divided into the colloid and tubular type of carcinoma. All cases with predominant fistulous tracts into the adjacent organs and a minor component of focal invasive carcinoma were classified as the fistulous extension type. The pathology materials of each case included 10 to 20 sections containing the hematoxylin-eosin-stained tumor. The slides were carefully reviewed with special attention being paid to the presence or absence of an invasive carcinoma component. A review of the clinical data of each case included the post-operative tumor recurrence, patient survival and the follow-up period.
A representative formalin-fixed, paraffin-embedded block of the tumor tissue was selected from each case for the immunohistochemical study, and stained using the conventional avidin-biotin-peroxidase complex (ABC) method with the following antibodies; MUC1 (Novocastra monoclonal, 1:50 dilution) and MUC2 (Novocastra monoclonal, 1:50 dilution). For two antibodies, the cytoplasmic immunoreactivity in more than 10% of the cells was considered to be "expression".

RESULTS

A total of 68 cases of IPMT were retrieved from the pathology files. The cases consisted of 20 adenomas, 16 moderate dysplasias, 16 non-invasive carcinomas and 16 invasive IPMTs. Among the 16 cases of the invasive type IPMT, there were eight colloid and six tubular types of carcinomas. The remaining two cases showed multiple fistulous extensions into the stomach, intrapancreatic bile duct and duodenum. Both cases showed foci of carcinoma in-situ and microscopic invasive carcinoma components of either a colloid or tubular type within the pancreas and around the fistulous tracts. The gross finding of the invasive IPMT of a colloid or tubular type was a mass with cysts or ductal ectasia filled with mucin. The cases with the fistulous extension type did not present as masses but as cystically dilated fistulous tracts into the stomach and duodenum and the diffuse dilation of the main and branch ducts. Fig. 1-3 show representative figures of the gross and microscopic features.

Recently, a consensus for histological subtype classification of pancreatic IPMT was established. When separated according to the histological subtype, our cases of malignant IPMT were classified into 12 pancreatobiliary and four intestinal types, which
comprised one colloid type, one tubular type and two fistulous extension types.

IHC expression of the invasive IPMT for MUC1 and MUC2 was comparable to their histological subtypes. MUC1 was positive in seven (87.5%) out of eight colloid and in five (83.3%) out of six tubular types. However, there was no IHC expression of MUC1 in the two fistulous extension types, which showed only MUC2 expression. Table 1 summarizes the IHC mucin profiles according to the invasive type of malignant IPMT and Fig. 4 shows the representative figures.

The follow-up data from 6 to 52 months duration were available in all cases. Five patients died during the follow up period. Two patients had recurrences in the remnant pancreas and two patients developed cancer peritonei. One patient died from a liver
metastasis. The mean survival duration was 14 months in the patients with IPMT related death. Histologically, three were the colloid type, two were the tubular type, and all were of the pancreatobiliary type. Of the two cases with a fistulous extension, one patient had a multiple abdominal lymph node metastasis two months after surgery. However, the other patient had no tumor recurrence or distant metastasis during a follow up period of 15 months. Statistical analysis of the survival rate according to the different growth patterns of malignant IPMT showed no association. Table 2 shows the clinicopathological characteristics.

**DISCUSSION**

IPMT is a distinct type of intraductal pancreatic tumor that has been differentiated from other neoplasms of the pancreas. The gross and microscopic appearances of these tumors are dependent upon the interplay between two factors: epithelial proliferation and mucinous secretion. When the former predominates, the...
result is a multicentric involvement of the major ducts by a predominantly papillary lesion. When there is instead a predominance of mucinous secretion, the result is a gross dilation of the ducts, which appear filled with mucus. IPMTs with a non-invasive carcinoma usually shows diffusely duct dilatation without a mass lesion. When an invasive carcinoma develops, it usually presents as a mass lesion. Our cases with the colloid or tubular type presented as masses with a mucin-filled cystic dilation or ductal ectasia.

The gross and microscopic appearances of IPMT with a fistulous extension were different from those of conventional invasive IPMT. They were grossly non-mass forming but showed easily recognizable fistulous tracts. The microscopic evaluation revealed the intraluminal growth of the papillary-mucinous epithelium within the gastric and duodenal mucosa. A preoperative duodenoscopy showed the mucin secretion in the gastric or duodenal mucosa of either case. However, biopsies were not taken at these sites with mucin secretion. The post-operative microscopic examination of our cases with a fistulous extension revealed gastric or duodenal involvement by the papillary-mucinous epithelium with moderate to severe dysplasia rather than an overt carcinoma (Fig. 5A). An examination of the pancreatic side could identify foci of carcinoma in-situ and microscopic invasive carcinomas in the dilated ducts (Fig. 5B). Therefore, it may be difficult to consider a diagnosis of IPMT with a fistulous extension on the endoscopic biopsy alone but the presence of a dysplastic papillary-mucinous epithelium outside the pancreas along with the endoscopic findings of mucin secretion outside the ampulla of Vater and the radiological findings of fistulous tracts to the adjacent organs are indicative of this rare form of malignant IPMT. Recently, we encountered another interesting biopsy material in which the initial impression was a gastric invasion by pancreas cancer. The radiological impression was not that of a malignant IPMT but an ordinary ductal adenocarcinoma with an abnormal extension to the stomach. However, the microscopic findings of a gastric biopsy were an abnormal papillary-mucinous epithelium with moderate to severe dysplasia (Fig. 6). Based on our experience, we could suspect that abnormal papillary-mucinous epithelium of the gastric mucosa was the fistulous extension of malignant IPMT, and main mass of the pancreas might be an advanced invasive IPMT.

Different mucin profiles according to the histological subtype classification of IPMT have been reported. This study showed similar mucin profiles of invasive IPMTs to those previously reported. The fistulous extension type IPMT showed more common MUC2 expression than the invasive types. However, the number of cases was too small to indicate significance.

It was believed that IPMT with overt invasion outside the pancreas had a poor prognosis, being similar to ductal adenocarcinoma of the pancreas. Kurihara et al suggested that IPMT with biliopancreatic fistula has a comparatively favorable prognosis. However, the clinical outcome of IPMTs with pancreatobiliary and pancreatodigestive fistulae is unclear. Our two patients with fistulous extension growth showed different clinical courses despite having identical histological or IHC mucin profiles. Therefore, the observation of more cases will be needed to better understand the biological behavior of this unusual IPMT.

In conclusion, malignant IPMT of the pancreas showed different growth patterns including growth invasion and fistulous extension to the adjacent organs. Because of the rarity of the fistulous extension type, the fistulous lesions of IPMT can be misinterpreted as a non-neoplastic inflammatory tissue reaction on a preoperative radiological evaluation as well as in the surgical field, or may be overlooked in a histopathological evaluation. IPMT with a fistulous extension should be regarded as an important unusual growth pattern of a malignant IPMT of the pancreas and an awareness of this unusual type is important not only to pathologists but also to radiologists and clinicians.

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