

Prevalence and Clinicopathologic Features of Mucinous Cystic Tumor and Intraductal Papillary Mucinous Tumor of Pancreas in Korea

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Background : Mucin producing cystic neoplasms, such as mucinous cystic tumor (MCT) and intraductal papillary mucinous tumor (IPMT) of the pancreas, are uncommon but become increasing in their incidences. The pathologic classification and biologic potential of these neoplasms remain the subject of controversy. **Methods :** The Gastrointestinal Pathology Study Group of the Korean Society of Pathologists analyzed the clinicopathologic characteristics of 85 cases of MCT and 72 cases of IPMT and examined the expression patterns of p53, CEA and MUC1. **Results :** IPMT was located largely in the head, and showed connection with the main pancreatic duct (MPD, 68.1%), no ovarian-like stroma (0/72), and presence of intervening intratumoral normal or atrophic parenchyma. On the other hand, MCT was located largely in the tail (73%), and showed common ovarian-like stroma (66/80), rare connection with the MPD (7/85) and no intervening pancreatic parenchyma. CEA and p53 immunoexpressions were significantly increased from adenoma through borderline to carcinoma, but MUC 1 was expressed only in the invasive carcinoma among cases of MCT and IPMT. **Conclusions :** The tumor location, ovarian-like stroma, connection with the MPD and intratumoral intervening nonneoplastic tissue were helpful in the differential diagnosis between IPMT and MCT. CEA and p53 expressions can be indicators of malignancy, while MUC 1 expression can indicate invasion.

Key Words : Mucinous Cystic Tumor-Intraductal Papillary Mucinous Tumor-Pancreas

INTRODUCTION

Cystic neoplasms of the pancreas are rare and have relatively similar characteristics on modern imaging modalities.^{1,2} But the incidences of these cystic neoplasms have been increasing, and the origin of the neoplastic cells and their biologic aggressiveness are still controversial.^{1,3-17} The spectrum of cystic neoplasms encompasses biologically diverse diseases and can be categorized into serous tumor, mucinous cystic tumor (MCT) and intraductal papillary mucinous tumor (IPMT).^{1,18} IPMT and MCT are classified as separate categories of pancreatic exocrine tumor.^{3,19} It has been known that these tumors are potentially malignant, but have good prognosis.^{3,18,20,21} The recognition and differentiation of MCT and IPMT from other cystic disorders of the pancreas are crucial because of their malignant potential.¹ However, differential diagnosis between IPMT from MCT remains a

challenge because clear criteria for differentiation have not been established yet, and clinical manifestations are variable and not correlated with the pathologic features. In MCT and IPMT, there are both adenoma and carcinoma lesions, but it is not always possible to differentiate the two lesions, especially before surgical resection. Thus, some authors have suggested that the pathologic features such as degree of cellular atypism and stromal invasiveness should be used as prognostic factors.²¹⁻²³ Several previous reports suggested the presence of adenoma-carcinoma sequences in these neoplasms.^{21,24-27}

In Korea, the incidence of mucin-producing cystic neoplasms of the pancreas is very low.²⁸ Moreover, the clinical characteristics, prevalent sites, macroscopic and microscopic findings and prognostic factors have yet to be clarified. Therefore, the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists collected cases of MCT and IPMT from hospitals throughout the

country. We then examined clinicopathologic features, including degree of histopathologic abnormalities and prognosis, and immunorepressions of CEA, p53 and MUC1 to identify their diagnostic values.

MATERIALS AND METHODS

Materials

This study included surgically resected 157 cases of pancreatic mucin producing cystic neoplasms from January 1990 to June 2000 that were retrieved from the files of the department of pathology of 21 hospitals located in different parts of Korea. They were composed of 85 cases of MCT and 72 cases of IPMT. Cases lost during follow-up, cases without exact clinicopathologic data, cases with indefinite data, recent cases, and cases of ductal carcinoma showing cystic change were discarded.

Methods

Evaluation of clinicopathologic findings

A committee reviewed the slides and collected representative slides having the highest degree of dysplasia, well preserved blocks and clinicopathologic data as well as radiological findings from the hospital records and from pathologic reports. Subsequently, committee members reviewed the slides all together several times with 10 head microscopes. Each case was then divided into MCT and IPMT, and classified into adenoma, borderline, non-invasive carcinoma or invasive carcinoma. We correlated these data with the other clinicopathologic parameters and follow-up data. For standardizing the clinicopathologic features, we made a common data sheet containing age, sex, symptoms and signs, radiologic and pathologic features. Pathologic diagnosis and classification were done according to WHO classification.¹⁴

Immunohistochemical staining

Immunohistochemical staining was performed in 101 cases following the standard avidin-biotin peroxidase conjugate method. At first, several 4 μ m-thick sections were obtained from the paraffin-embedded tissue blocks. They were deparaffinized in xylene and rehydrated in graded concentrations of alcohol. Endogenous peroxidase activity was blocked by treating the sections with 0.3 % hydrogen peroxide for 5 minutes. In cases of p53 and MUC1, sections were treated in a microwave oven for 10 minutes for antigen retrieval. For CEA the pretreatment was not done. They were

Table 1. Antibodies used for immunohistochemical stain

Antibody	Source	Dilution	IP*
CEA	DAKO monoclonal, CA, U.S.A.	prediluted form	40 min.
p53	DAKO monoclonal DO-7, CA, U.S.A.	prediluted form	40 min.
MUC1	Novocastra Laboratory Ltd, UK	$\times 200$	40 min.

*IP: incubation period.

treated with different primary antibodies for 40 minutes (Table 1). A Chem Mate™ Envision™ detection kit (DAKO Corporation, CA, USA) was used for secondary antibody at room temperature for 30 minutes. We used 3,3-diaminobenzidine for visualizing the immunoreaction, and Mayer's hematoxyline for counterstaining. Colonic adenocarcinoma was used as a positive control for CEA, and mammary carcinoma was for p53 and MUC1. Normal serum was used instead of primary antibodies for negative controls.

Interpretation of immunohistochemical staining

When a definite brown nuclear staining was present for p53, regardless of the staining intensity, it was considered positive, but cells with very weak equivocal staining were considered negative. Staining patterns of the diffuse type (positive staining in most areas) or nested type (positive staining in cell nests composed of more than 20 cells) were regarded as having p53 overexpression. Cases showing positive reactions in less than 10% of the cells were considered as negative. Diffuse cytoplasmic stainings for MUC1 and CEA were considered as positive. Cases showing only luminal positivity and positive reaction in less than 10% of cells were considered as negative. Quantitative grading was not done.

Statistical analysis

Statistical analysis was performed using the SAS procedures for means, t-test and univariate analysis (SAS institute, Carry, NC, U.S.A.). We computed the mean, standard deviation and correlation coefficient of each feature using Spearman's nonparametric correlation test. The student's t-test was used to determine the significance of parameters. Probability values less than 0.05 were considered statistically significant.

RESULTS

Clinicopathologic findings

Patients included 50 men and 107 women (M:F=1:2.1) with a mean age of 53.02 (range 5-92) years (Table 2). According to

the tumor type, MCT was more common in women ($p < 0.0001$) and IPMT was slightly more common in men. Clinical symptoms varied with abdominal pain being the most common symptom (41 cases). The other symptoms were anorexia (30 cases), abdominal discomfort (20 cases), and a palpable mass (16 cases). Twenty-one cases were incidentally detected. Pancreatitis was associated only in 39 cases of IPMT out of 91 cases with abdominal symptoms.

Macroscopically, MCTs were unilocular or multilocular cystic tumors containing abundant mucinous material. Adenoma cases were largely unilocular, and became multilocular more frequently in malignant cases. Connection with the main pancreatic duct (MPD) was noted in 7 cases (8.2%), was absent 64 cases (75.3%) and was not described in 14 cases. The tumor size was variable, ranging from 1 cm to 31 cm (mean: 6.88 cm); the mean sizes of adenoma (5.96 cm), borderline (6.68 cm), non-invasive carcinoma (4.23 cm) and invasive carcinoma (10.62 cm) suggested an

Table 2. Clinicopathologic characteristics of intraductal papillary mucinous tumor and mucinous cystic tumor

	MCT	IPMT
Age	5-92 (mean 46.47)	32-77 (mean 60.87)
Sex (M:F)	9:76	41:31
Size	1-31 cm (6.88 cm)	0.7-23 cm (5.76 cm)
Pancreatitis	0/28	39/63
Gross	Uni or multilocular cyst	multiple cyst
Connection with MPD	7/85	49/72
Lining cell	mucus containing cuboidal/columnar	mucus containing cuboidal/columnar
Ovarian type stroma	66/80	0/72
NLP between cyst	1/85	72/72

MCT, mucinous cystic tumor; IPMT, intraductal papillary mucinous tumor; MPD, main pancreatic duct; NLP, normal pancreatic tissue.

Table 3. Distribution of mucinous cystic neoplasm of pancreas according to the site

Pathologic diagnosis	Head	Body	Tail*	Whole	NS	Total
MCT	9	5	62	2	7	85
Adenoma	8	2	33	0	5	48
Borderline	1	1	15	1	0	18
Non-inv Carcinoma	0	1	4	0	0	5
Inv Carcinoma	0	1	10	1	2	14
IPMT	29	8	23	9	3	72
Adenoma	3	4	1	0	0	8
Borderline	19	3	9	1	2	34
Non-inv Carcinoma	7	1	10	7	0	25
Inv Carcinoma	0	0	3	1	1	5

*: Cases arising in body-tail or tail of the pancreas. MCT, mucinous cystic tumor; IPMT, intraductal papillary mucinous tumor; Non-inv, non invasive; Inv, invasive; NS, not specified.

increasing tendency of the tumor according to the malignant potential. The tumor size was not described in 16 cases (Table 2). The tail was the commonest site in MCT (62 cases), especially in adenoma cases, while carcinoma cases had a tendency to involve the whole pancreas (Table 3).

IPMTs showed diffuse or segmental dilatation of the MPD with abundant mucin secretion. Connection with the MPD was noted in 49 cases (68.1%) and uncertain in 23 cases. The tumor size of IPMTs ranged from 0.7 cm to 23 cm (mean: 5.76 cm); the mean sizes of adenoma, borderline, non-invasive carcinoma and invasive carcinoma were 4.73 cm, 6.36 cm, 5.43 cm and 8.75 cm, respectively, which exhibited no difference according to the malignant potential. The tumor size was not described in 10 cases. IPMT mainly involved the head and the tail (Table 3).

Microscopically, the cyst wall of MCTs consisted of thick fibrous

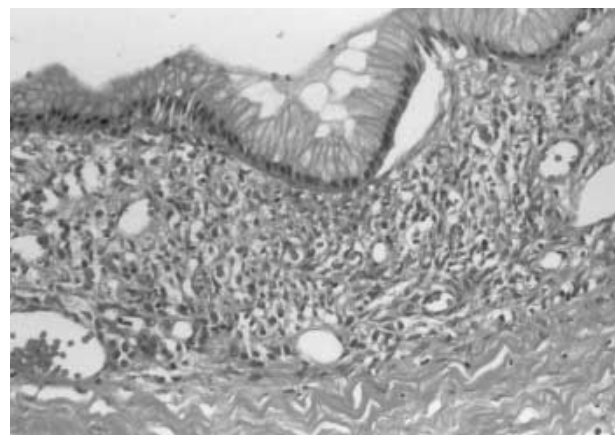


Fig. 1. Adenoma of mucinous cystic tumor. Mucin containing tall columnar lining epithelial cells with basally located nuclei are noted. Subepithelial layer exhibits ovarian-like stroma.

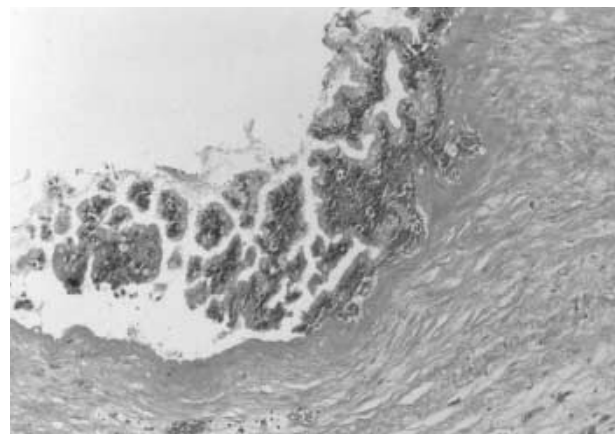


Fig. 2. Borderline mucinous cystic tumor. Papillary epithelial cells showing low or moderate cellular atypia are present.

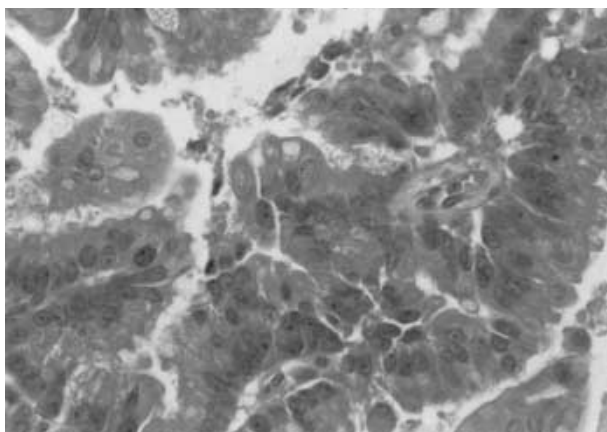


Fig. 3. Non-invasive malignant mucinous cystic tumor. Severe cellular atypia with hyperchromatic nuclei and frequent mitosis are noted.

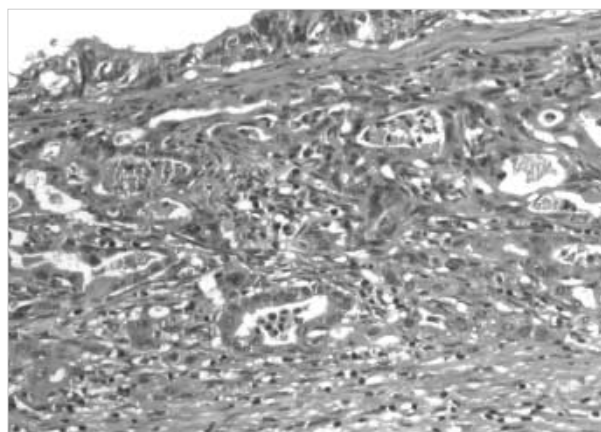


Fig. 4. Invasive malignant mucinous cystic tumor. Stromal invasion by the atypical cells and glands is noted.

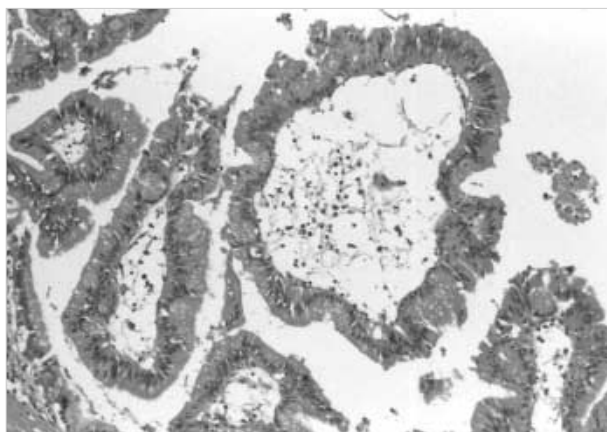


Fig. 5. Adenoma of Benign intraductal papillary mucinous tumor. Dilated duct containing papillary structure is noted. Papillae are lined by mucin containing tall columnar cells without cellular atypia. Ovarian-type stroma is not present.

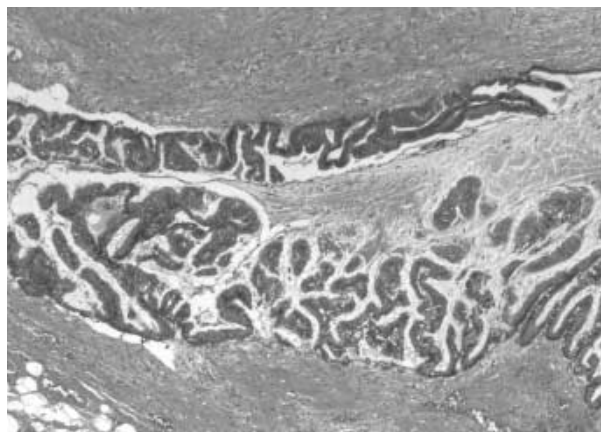


Fig. 6. Borderline intraductal papillary mucinous tumor. More complex papillae with stratified columnar cells are noted.

tissue, which was partly hyalinized and partly composed of cellular stroma with spindle cells resembling ovarian stroma. All of the MCTs had cuboidal or columnar lining epithelial cells with areas of papillary projections. The amount of mucin, degree of proliferation and atypia of the neoplastic cells were various from case to case and from area to area within the tumor (37/85 cases). In adenomas, cuboidal cells without cellular atypia lined the cyst walls. Most of the cases did not have papillary structures with fibrovascular cores. Nuclei were located mainly in the basal portion, and pseudostratification was not noted (Fig. 1). Ovarian-type stroma was noted in 34 cases (79%) out of 43 cases. Normal or atrophic pancreatic tissue within the tumor was noted in only one case. In 18 cases of borderline MCTs, most cases exhibited papillary structures lined by columnar epithelia with low or moderate degree of cellular atypism (Fig. 2). Ovarian-type stroma was

noted in 13 cases (72%) out of 18 cases. Five cases were non-invasive carcinomas of MCT, which exhibited a definite malignant change of epithelial cells with cellular proliferation, hyperchromasia, decreased mucin, frequent mitosis and nucleoli without evidence of invasion (Fig. 3). Ovarian-like stroma was noted in all cases. Fourteen cases were invasive carcinomas showing ovarian-type stroma with severe cellular atypia and diffuse invasion (Fig. 4). Four men and ten women did not have ovarian-type stroma, which suggested that ovarian-type stroma was not concomitant in all MCTs, even in female patients.

IPMT exhibited no ovarian-type stroma in all cases. IPMTs consisted of papillary proliferation of cuboidal or columnar epithelial cells with small fibrovascular stalks. The cytoplasmic features and grades of cellular atypia of these neoplastic cells varied from case to case and from area to area within the tumor (62/72 cases). Adenoma cases of IPMT showed dilated ducts having papillary

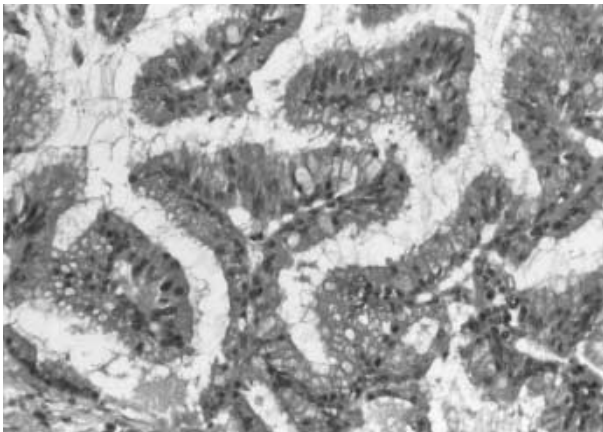


Fig. 7. Borderline intraductal papillary mucinous tumor. Lining cells show enlarged and stratified nuclei with moderate cellular atypia and upward location.



Fig. 8. Non-invasive malignant intraductal papillary mucinous tumor. More complex and proliferative papillae are present in the dilated ducts. Atrophic pancreatic tissue is noted within the neoplasm.

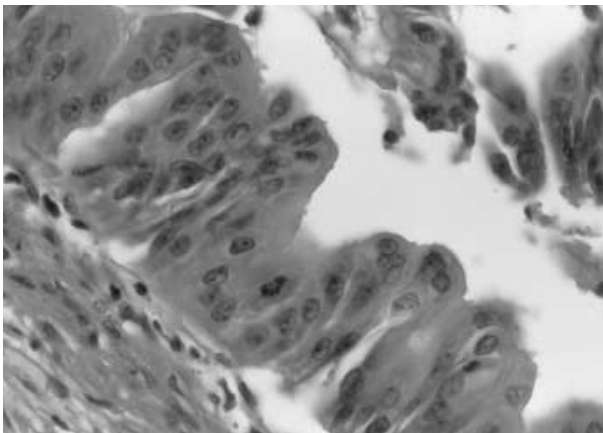


Fig. 9. Non-invasive malignant intraductal papillary mucinous tumor. Tumor cells show severe nuclear atypia, prominent nucleoli and hyperchromasia with many mitosis. Ovarian-type stroma is not present.

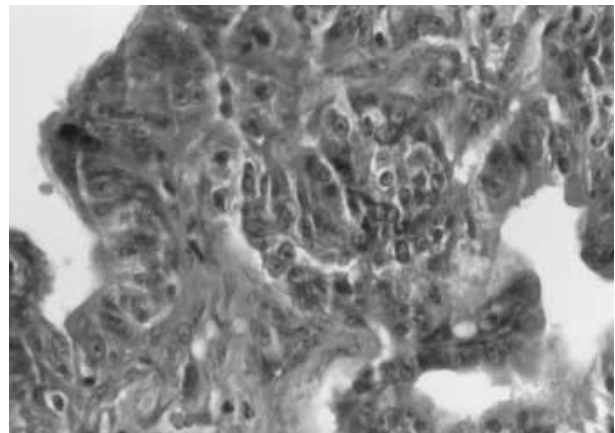


Fig. 10. Invasive malignant intraductal papillary mucinous tumor. Stromal invasion by the malignant cells is present.

proliferation of cuboidal mucin-producing cells (Fig. 5). Between these dilated ducts, there was normal or inflamed atrophic pancreatic tissue. Cellular atypism or cellular crowding was not identified. Borderline IPMT showed stratified cuboidal epithelial cells having moderate atypism in all 34 cases (Fig. 6). Nucleoli were enlarged and stratified and moved upward from basal locations (Fig. 7). Adenoma area was accompanied in many cases. One case exhibited diffuse borderline IPMT features in the liver, even though borderline lesions were focally noted in the pancreas with the background of adenoma. Carcinoma cases of IPMT exhibited severe nuclear atypism, irregular nuclear arrangement, prominent nucleoli, hyperchromasia and frequent mitosis (Fig. 8, 9). Invasion was noted in 5 cases. In those cases, stromal fibrosis, edema and inflammatory cell infiltration were noted as reactions

to invasion (Fig. 10). One invasive carcinoma case showed squamous metaplasia. The amount of mucin in the cytoplasm was inversely correlated with the increase of malignancy.

We followed-up 122 cases for 1 to 126 months. Among them, 104 subjects were alive and 18 subjects were dead. The latter group consisted of 4 adenomas of MCT, 3 borderline MCTs, 2 invasive carcinomas of MCT, 3 adenomas of IPMT, 3 borderline IPMTs, and 3 non-invasive carcinomas of IPMT, which showed no statistically significant correlation between types of tumor and survival. The causes of death in the adenoma patients with MCT and IPMT were not directly related to the tumor: Four patients died within 3 months after operation due to postoperative complications. One patient with adenoma (1.3 cm) of IPMT died 15 months after operation with an unrelated cause; one patient with a 9.5 cm-sized adenoma of MCT, had died 2 years after operation.

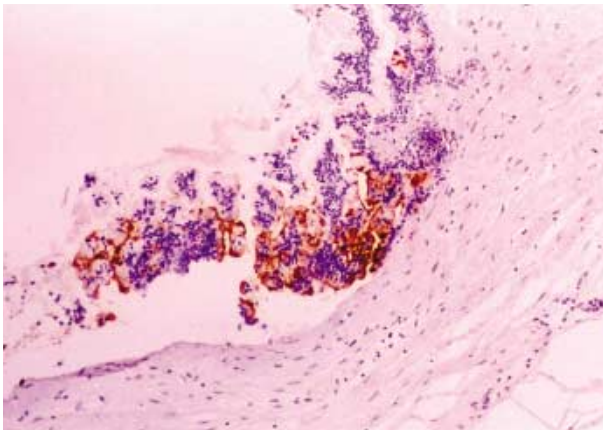


Fig. 11. Intracytoplasmic expression for CEA is noted in the papillary epithelial neoplastic cells of borderline mucinous cystic tumor.

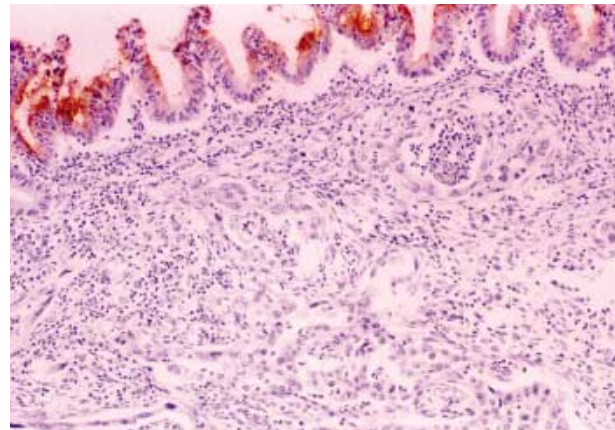


Fig. 12. Invasive malignant mucinous cystic tumor. Immunohistochemical expression for CEA is noted in the malignant epithelial cells. But invasive portion does not show positive reaction.

Table 4. Immunohistochemical expression of the mucinous cystic tumors and intraductal papillary mucinous tumors

Type	No.	CEA No. (%)	p53 No. (%)	MUC1 No. (%)
MCT	55	11 (20.0)*	9 (16.4)*	10 (18.2)**
Benign	24	0 (0.0)	0 (0.0)	0 (0.0)
Borderline	14	3 (21.4)	1 (7.1)	0 (0.0)
Non-inv Carcinoma	3	0 (0.0)	0 (0.0)	0 (0.0)
Inv Carcinoma	14	8 (57.1)	8 (57.1)	10 (71.4)
IPMT	46	11 (23.9)	0 (0.0)	4 (8.7)**
Benign	5	0 (0.0)	0 (0.0)	0 (0.0)
Borderline	20	4 (20.0)	0 (0.0)	0 (0.0)
Non-inv Carcinoma	17	4 (23.5)	0 (0.0)	0 (0.0)
Inv Carcinoma	4	3 (75.0)	0 (0.0)	4 (100)

MCT, mucinous cystic tumor; IPMT, intraductal papillary mucinous tumor; Non-inv, non-invasive; Inv, invasive; *, $p < 0.05$ at the Chi-Square test (Likelihood Ratio) between adenoma, borderline, non-invasive carcinoma and invasive carcinoma, **, $p < 0.05$ at the Chi-Square test (Likelihood Ratio) between invasive carcinoma and other categories.

We could not obtain the information pertaining to the remaining 1 case. Borderline and carcinoma cases revealed tumor-related deaths.

Immunohistochemical findings

Immunohistochemical stainings for p53, CEA and MUC1 were done in 55 cases of MCT and 46 cases of IPMT (Table 4).

In cases of MCT, CEA was positive in 11 cases (20.0%), p53 in 9 cases (16.4%) and MUC1 in 10 cases (18.2%). A gradual stepwise increase in the frequency of overall expression of CEA and p53 was observed with the increase of cellular atypia from adenoma to carcinoma ($p < 0.05$) (Fig. 11-13). In cases of invasive carcinoma, both invasive and non-invasive areas showed positive reactions to CEA. But one case exhibited positive immunoexpres-

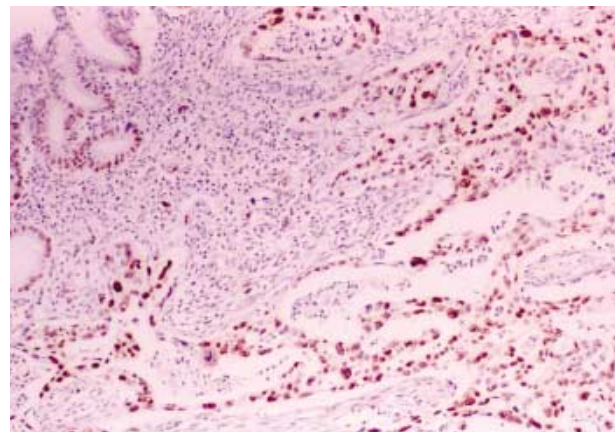


Fig. 13. Invasive malignant mucinous cystic tumor. Immunohistochemical stain for p53 shows positive nuclear stain both in the invasive portion and lining malignant cells.

sion only in non-invasive area. On the other hand, MUC1 was expressed only in the invasive carcinoma cases ($p < 0.05$) (Fig. 14). Correlations of the immunohistochemical expression showed statistical significance between p53 and MUC1 ($p < 0.05$), between CEA and MUC1 ($p < 0.05$), and between CEA and p53 ($p = 0.001$).

In cases of IPMT, CEA immunohistochemical expression also increased from adenoma through borderline to carcinoma, which was statistically insignificant ($p = 0.056$) (Fig. 15). We were unable to evaluate p53 immunohistochemical expression, because there were no positive cases. MUC1 immunohistochemical reactivity was positive only in invasive carcinoma cases, which was statistically significant ($p < 0.05$) (Fig. 16). MUC1 immunohistochemical expression also correlated significantly with that of CEA ($p = 0.022$). Therefore, CEA and p53 immunohistochemical reactivities were helpful in identifying the degree of malignancy in MCT, and MUC1 immunohistochemical reactivity was a useful marker for invasion

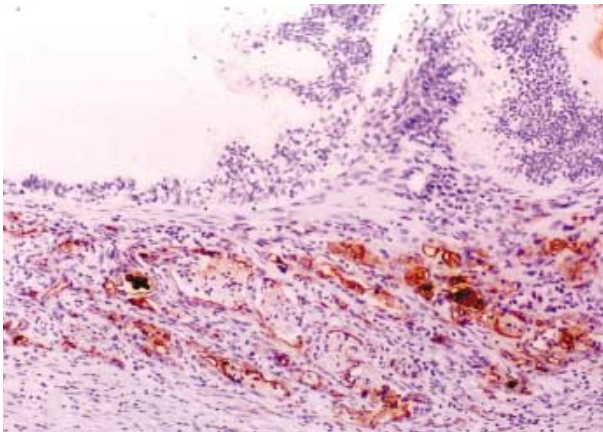


Fig. 14. Invasive malignant mucinous cystic tumor. Immunopositivity for MUC1 is noted only in the invasive neoplastic cells.

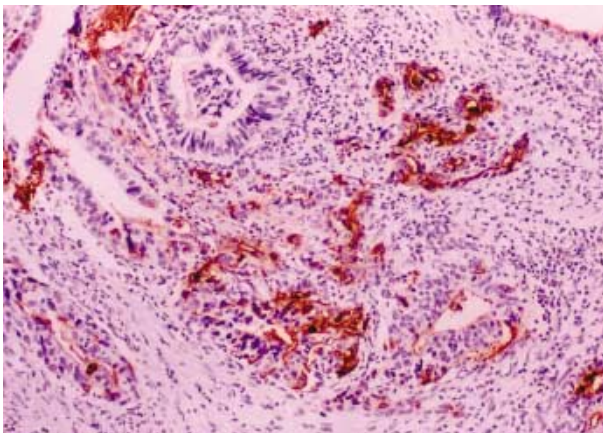


Fig. 16. Invasive malignant intraductal papillary mucinous tumor. Strong cytoplasmic immunopositivity for MUC1 is noted only in the invasive neoplastic cells.

in both MCT and IPMT.

DISCUSSION

Our study showed that IPMT developed largely in the head and the tail of the pancreas of older men and MCT developed in the tail of middle-aged women. This result was identical to other reports.^{20,21,24,26} Ovarian-type stroma was present in 66 cases (82.5%) out of 80 cases of MCT, but none of the 72 cases of IPMT showed ovarian-type stroma. These results were also in line with other reports^{3,20} and the ovarian-type stroma is one of the histological differential points between IPMT and MCT. Moreover, there was intervening atrophic or normal-appearing pancreatic tissue between cystic neoplastic lesions in all cases of IPMT, while

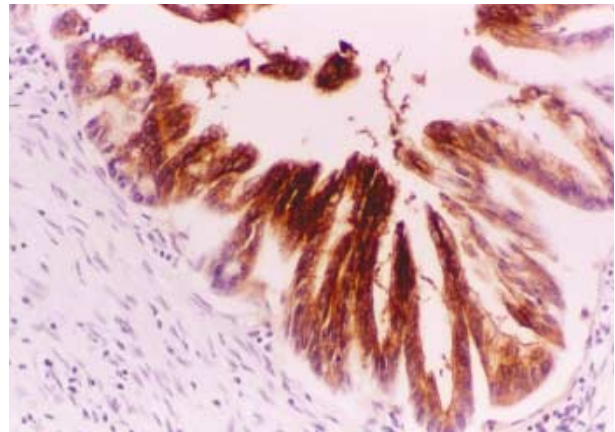


Fig. 15. Non-invasive malignant intraductal papillary mucinous tumor. Strong cytoplasmic immunopositivity for CEA is present.

only in one case of MCT. Therefore, this feature is one of the histological points for differential diagnosis between the two. However, there is no identifiable report that definitively describes this feature as a differential point. Many cases of both MCT and IPMT showed variable grades of atypism from borderline to invasive carcinoma in the tumor according to the site. This result agrees with other reports.^{1,4,12,20,21} Thus, it suggested that a careful and thorough examination of sections should be mandatory for accurate diagnosis. Although there are some difficulties in differentiating branch-type IPMT from MCT macroscopically and microscopically,^{21,27} clinicopathologic features such as location, presence of ovarian-type stroma and intercytic pancreatic tissue, connection with the MPD are very helpful features for differential diagnosis. Therefore, a definite diagnosis requires the careful exploration of clinical findings and macroscopic and microscopic features.

The difference of the prognoses between patients with IPMT and MCT was not statistically significant. Overall prognosis was good with only 18 deaths out of 122 cases. Among the deaths, tumor grade and type were similar, and causes of death were not related with the tumors in some cases. These results were similar those of other reports.^{20,21,23,27}

The immunohistochemical examination showed very meaningful results. In MCT, CEA and p53 immunopositivities increased from adenoma through borderline to carcinoma, which was statistically significant. Benign and normal ductal epithelial cells showed only weak positive reactions for CEA, along the luminal border but the transition to diffuse cytoplasmic expression was noted in the site of the malignant transformation. These results are in line with previous reports.^{5,6,11,12} In one case of invasive carcinoma, a positive reaction was noted only in the non-invasive

area. But other cases showed positive reactions in both invasive and non-invasive areas. This pattern was not described in other reports, suggesting the need for further study. In IPMT, CEA immunoreaction increased from adenoma through borderline to carcinoma, which was not statistically significant. This result is in accord with that of the previous study.¹¹ As with MCT, MUC1 was expressed only in cases of invasive carcinoma, which corresponds with those of the previous reports,^{8,9,16} and suggests that MUC1 is a good marker for the evaluation of invasion. Therefore, CEA and p53 expressions are helpful for grading these neoplasms because their immunoreactions increase with the increase of atypism. On the other hand, MUC1 is helpful for the evaluation of invasion.

In conclusion, MCT and IPMT showed varied degrees of atypism and proliferation in and between tumors, suggesting the need for the thorough and careful examination of sections. We also found that several features such as presence of nonneoplastic parenchyma between dilated ducts, tumor location, connection with the MPD and presence of ovarian-type stroma were very useful for the differentiation between MCT and IPMT. Moreover, CEA, p53 and MUC1 appeared to be good markers for evaluating atypism and prognosis.

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