10.1053.paor.2000.0263 available online at http://www.idealibrary.com on IDEAL

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Pre-existing Histological Type and Developmental Mechanism of Mucinous Noncystic Carcinoma of Pancreas

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Eleven cases with mucinous noncystic carcinoma (MC) of the pancreas were studied by histology and mucin immunohistochemistry, to elucidate the mechanism, or route of development, and pre-existing histological type of MC of the pancreas. These MCs were observed in close approximation to, or surrounding, intraductal papillary-mucinous carcinomas (IPMCs), and were centrally situated among ductal adenocarcinomas (DAs). Hence, the 11 cases originated from 8 IPMCs and 3 DAs. The mechanism and routes to MC were divided into four types as follows: IPMC directly invaded the stroma (4 cases), over-production of mucin in IPMC expanded the branches of the pancreatic duct possibly resulting in rupture (3 cases), DA underwent extreme mucinous degeneration (3 cases), and a recurrent form, as MC, at the surgical stump of IPMC (one case). The outcomes of MC cases with IPMC had variable survival rates, while those from DA had short durations. MUC immunoreactivity in MC was divided into three categories; anti-MUC1-positive only (2 IPMCs, 2 DAs), mixed anti-MUC1 and anti-MUC2-positive (3 IPMCs, one DA) and anti-MUC-positive only (3 IPMCs). Pre-existing MC histological types included both IPMC and DA. These two pre-existing types of MC involved mucin overproduction and mucinous degeneration. MUC immunoreactivity in MC revealed three patterns, which may be related to variable outcomes. (Pathology Oncology Research Vol 6, No 2, 125–129, 2000)

Keywords: pancreas cc, intraductal papillary-mucinous cc, ductal adenocc, mucin overproduction, mucinous degeneration, MUC immunoreactivity

Introduction

The majority of pancreatic carcinomas are ductal adenocarcinomas (DAs), with marked desmoplasia. Among the pancreatic carcinomas, mucinous noncystic carcinoma (MC), or colloid carcinoma, is a variant of DA and is uncommon, comprising between 1% and 3% of all carcinomas of the pancreas.[1] According to the AFIP fascicle by Solcia et al,[2] MC is characterized by abundant extracellular mucin production, which results in a gelatinous cut surface. Microscopically, MC shows large pools of mucin which are partially lined by well-differentiated cuboidal cells. The mucin lakes usually contain clumps or strands of tumor cells.

However, in recent years, intraductal papillary-mucinous carcinomas (IPMCs) with marked mucin production and cystic dilatation of the duct system, or intraductal papillary-mucinous tumors, has been described in the literature, particularly by Japanese authors.[3,4] The invasive components of some of the intraductal tumors may show features similar to those of MC.[5,6]

Recent studies have revealed that mucin is a high molecular weight glycoprotein with many oligo-glycoproteins connected to its protein skeleton. Recently, the nature of the core proteins, the mucin genes, and their peptide structures (MUC1 to MUC7) have been investigated.[7-9] Concerning pancreatic tumors, Osako et al[10] suggested that the expression of mammary type mucin core protein (MUCI) and intestinal type mucin core pro-

Received: Febr 28, 2000; *accepted:* April 14, 2000

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Abbreviations: MC, mucinous noncystic carcinoma; IPMC, intraductal papillary-mucinous carcinoma; DA, ductal adenocarcinoma.

 1219-4956/00/020125+05 $ 12.00/0

tein (MUC2) show a striking contrast between DA with a poor prognosis and IPMC with a favorable prognosis. Previously, MUC immunoreactivity for MC had not been investigated.

In this study, we examined MC in detail with MUC immunohistochemistry and investigated the route, or developmental mechanism, to MC from a pre-existing histological type of pancreatic carcinoma.

Patients and Methods

The subjects were 11 patients (9 men and 2 women) including one autopsied case with MC of the pancreas, with the following criteria; both abundant mucin or muconodules in the cut surfaces were recognized macroscopically, as well as cancer cells floating free in mucin lakes determined microscopically. The patients' ages ranged from 40 to 74 years (mean age, 59.6 years), and all, except for one autopsied case, underwent pancreatoduodenectomy or distal pancreatectomy for pancreatic carcinoma at our hospitals in the past 10 years. Of 11 patients, 3 also had diahetes and one had chronic pancreatitis, while none of the patients had any signs of paraneoplastic syndrome.

In each tumor, 2 to 7 cut surfaces were available for macroscopic study per case, with an average of 4.8 slices. Pancreatic tissue was fixed in 10% formaldehyde solution and processed into paraffin sections. Four to 17 tumor blocks per case were cut for study, with an average of 9.5 blocks. Four to 6 sections (3 μm thick) per block were prepared for histological stains [hematoxylin and eosin, periodic acid-Schiff (PAS), elastica van Gieson], and immunohistochemical examinations to anti-MUC1 (DF3, DAKO, CA, USA) (11) and anti-MUC2 (Cep58, Novocastra, Newcastle, UK).[12] In addition, the histological findings of fifty non-mucinous DAs as a control were compared with those of the tumors examined.

Results

In the present cases, the tumor tissues were recognized as having a gelatinous or colloid appearance at more than two cut surfaces. The histological findings showed rather well differentiated tubular adenocarcinomas admixing with carcinoma cells which were floating free in the mucin lakes. These MCs were observed in either close approximation to, or surrounding, the IPMC, and were centrally situated among the DA. The 11 cases were divided into two groups according to the pre-existing type of pancreatic carcinoma, as shown in *Table 1*, and were as follows; 8 MCs were derived from IPMCs (*Figures. 1,2*) including one patient who had recurrent MC at the surgical stump of a pancreatoduodenectomy due to IPMC (Case 5), while the remaining three originated from DAs, including the one autopsied case *(Figures. 3,4).* The 8 IPMCs had mainly spread intraductally by replacing the ductal epithelium, especially in Case 4, with marked extension to the branch of the pancreatic duct, and were clinically diagnosed as mucin-producing tumors[3,4] because of the overproduction of mucin by tumor cells and cystic dilatation of the pancreatic ducts. The 8 MCs were subdivided by developmental route as follows: 1) IPMC directly invaded the stroma via the wall of pancreatic ducts in an infiltrative nature and formed MC (4 cases), 2) IPMC caused a marked expansion of the branch pancreatic ducts, possibly resulting in rupture, creating muco-nodules with floating cancer cells in the surround-

Table 1. **Pre-existing type and MUC immunopositivity of mucinous noncystic carcinoma**

Cases	*Age*	*Sex*	*Location*	*Size (mm)*	*Operation*	*Pre-existing type and MUC immunoreactivity*	*MUC immuno-reactivity in MC*	*Prognosis (in months)*
1	66 yr	M	H	80x70x70	PD	IPMC; 2	1	Dead, 11 mo after surgery
2	60 yr	F	H	49x32x28	PD	IPMC; 1,2	1	Dead, 6 mo after surgery
3	73 yr	M	H	50x50x50	PD	IPMC; 1,2	1, 2	Dead, 10 mo after surgery
4	53 yr	M	B, T	65x50x30	DP	IPMC; 1,2	1, 2	Dead, 54 mo after surgery
5	68 yr	M	H	60x50x25	PD	(IPMC; 2)	–	Recurrent, 33 mo after the 1st surgery
	(recurrence)		B, T	60x60x55	DP	IPMC; 1,2	1, 2	Dead, 4 mo after the 2nd surgery
6	47 yr	M	H	35x20x20	PD	IPMC; 2	2	Alive, healthy 27 mo after surgery
7	61 yr	F	H	30x30x15	PD	IPMC; 2	2	Dead, 22 mo after surgery
8	71 yr	M	H	50x50x30	PD	IPMC; 2	2	Dead,* 3 mo after surgery
9	43 yr	M	H	40x35x30	PD	DA; 1	1	Dead, 6 mo after surgery
10	40 yr	M	T	37x35x30	DP	DA; 1,2	1, 2	Dead, 14 mo after surgery
11	74 yr	M	B, T	Huge tumor	Autopsy	DA; 1	1	Dead

H: head, B: body, T: tail, PD: pancreaticoduodenactomy, DP: distal pancreatectomy, IPMC: intraductal papillary-mucinous carcinoma, DA: ductal adenocarcinoma, MC: mucinous noncystic carcinoma. * Dead due to complications during postoperative course.

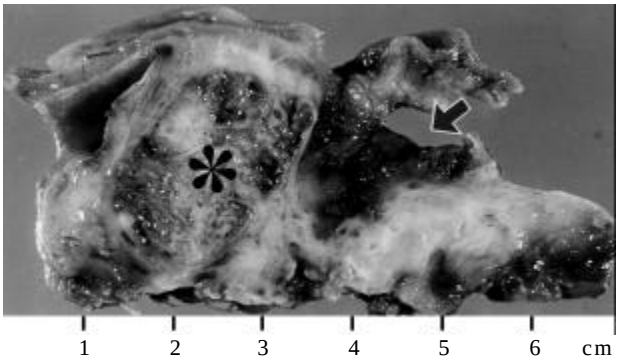

Figure 1. Macroscopic intraductal papillary-mucinous carcinoma (arrow) mainly in the main pancreatic duct showing well demarcated growth close to the mucinous noncystic carcinoma (asterisk) in a patient (Case 1; 66yr, M).

ing stroma (3 cases) (*Figure 5*), and 3) a remnant IPMC of the branch duct at the surgical stump of a pancreatoduodenectomy that recurred as MC (one case). The cytoplasms of the tumor cells in the intraductal component showed positive immunoreactivity for anti-MUC2 (*Figure 6*) mixed with or without anti-MUC1 immunopositivity, whereas those exhibiting MC patterns showed three different reactivities; anti-MUC1-positive only (2 cases) (*Figure 6*), mixed anti-MUC1 and anti-MUC2 positive (3 cases) and anti-MUC2 positive only (3 cases). The latter, DA accompanied by extreme mucoid degeneration, exhibited floating cancer cells in the mucin lakes, as shown in *Figure 4*. In one of the 3 DAs, the MC pattern was positively immunostained with mixed anti-MUC1 and anti-MUC2, whereas the remaining 2 cases showed positivity for anti-MUC1. These MUC immunoreactivities were almost negative in normal, non-diseased and hyperplastic pancreatic ducts. The postoperative courses of the MC cases are shown in *Table 1* and were as follows: among the 8 patients with pre-exsiting IPMC one lived for 27 months after surgery and 5 died, 6 to 54 months after surgery, except one patient who had a recurrence (Case 5), as mentioned above. One patient died due to postoperative complications (Case 8). The 2 remaining patients with DA, except the one autopsied case, died 6 and 14 months after surgery, respectively.

Fifty non-mucinous DAs as controls did not show abundant mucin in the cut surfaces of the tumors macroscopically, or floating cancer cells in the mucin lakes microscopically, and were immunostained positive with anti-MUC1 and negative with anti-MUC2 for cancer cells.

Discussion

The 11 pancreatic tumors examined in the present study were characterized by gelatinous or colloid cut surfaces and by floating cancer cells in the mucin lakes microscopically. These macroscopic and microscopic features of the tumors were judged using the AFIP criteria of Solcia et al[2] for MC, whereas 50 DAs as controls were not. According to Klöppel,[1] MC is a variant of DA. In this study, however, MC patterns in 8 of the 11 cases were observed in either close approximation to, or surrounding, the IPMC. These were clinically diagnosed as mucin-producing tumors[3,4] because of the marked mucin produced by the tumor cells and the cystic dilatation of the pancreatic duct. In the remaining 3 patients, MC patterns were centrally situated among the DA. Hence, MC was considered a variant of DA, and was similar to Klöppel's description of it.[1] Nevertheless, the invasive features of IPMC also showed a pre-existing type of MC. This finding was similar to that of several authors, as described below. According to Yamada et al,[5] 6 of 9 cases of infiltrative cancer (primarily papillary adenocarcinoma in the intraductal area) had muconodular infiltration patterns, while the other three cases showed tubular infil-

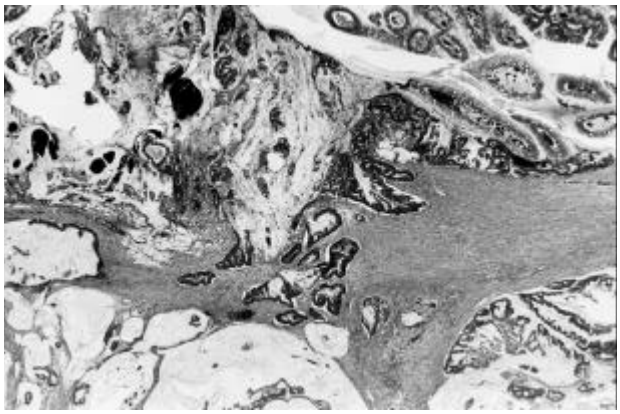

Figure 2. Intraductal papillary-mucinous carcinoma in the upper portion directly invading and forming a mucinous noncystic carcinoma in the stroma (the same case as in Figure 1.) HE stain x10.

Figure 3. Centrally mucinous degeneration in a grayish white, solid tumor (Case 9; 43yr, M).

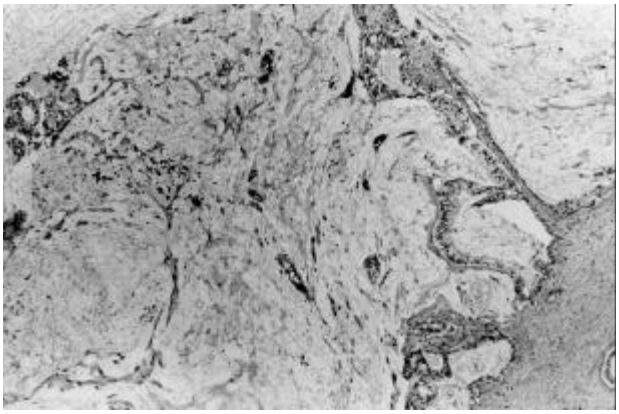

Figure 4. Floating cancer cells in the mucin lakes of a ductal adenocarcinoma (the same case as in Figure 3.) HE stain x40.

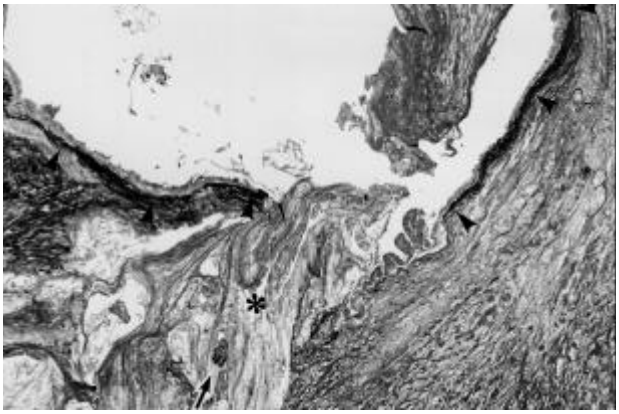

Figure 5. A branch of the pancreatic duct, identified by the ductal elastic fibers (arrowheads), was dilated markedly due to overproduction of mucin from IPMC and ruptured, resulting in a muconodular pattern with floating cancer cells (arrow) (Case 4; 53yr, M). Note the muconodular pattern (asterisk) which was not accompanied by the elastic fibers of the ductal wall. Elastica van Gieson stain, x50.

tration patterns. From these findings, they surmised that the muconodular infiltration pattern was the principal infiltration pattern of IPMC. Sessa et al[6] also observed 5 MCs, as invasive components, among 6 invasive IPMCs. Fukushima et al[13] observed five muconodular infiltrations in eight intraductal papillary tumors. Although these muconodular infiltrations did not always match the criteria of MC,[2] IPMC was considered one of the pre-existing histological types of MC. In this study, however, the developmental routes to MC were divided into three types as follows: IPMC directly invaded the stroma, IPMC expanded the branches of the pancreatic duct possibly resulting in rupture, and a recurrent form, as MC, at the surgical stump. In addition, according to our previous study,[14] intraductal carcinoma did not always show a papillary pattern or macroscopic mucin production with cystic dilatation of the duct system. Therefore, IPMC was the pre-existing type of MC and involved the overproduction of mucin, at least for MC, as an invasive feature.

On the other hand, MC cases from three DAs underwent extreme mucinous, or mucoid, degeneration, with floating cancer cells in mucin lakes. This finding was similar to Muir's description.[15] However, each MC and DA pattern was immunostained with anti-MUC1-positive only and also with mixed anti-MUC1 and anti-MUC2-positive as described below. Hence, the MC pattern was divided into two immunoreacting groups for anti-MUC1 and anti-MUC2.

Immunohistochemistry using anti-MUC1 and anti-MUC2[16] from duct-originating pancreatic tumors generally showed two patterns: the IPMC type showed negative anti-MUC1 and positive anti-MUC2 immunoreactivity, whereas the DA type showed positive anti-MUC1 and negative anti-MUC2 immunoreactivity. This was also described for non-invasive IPMC and DA by Osako et al.[10] They observed a striking contrast between the former with a favorable prognosis and the latter with a poor prog-

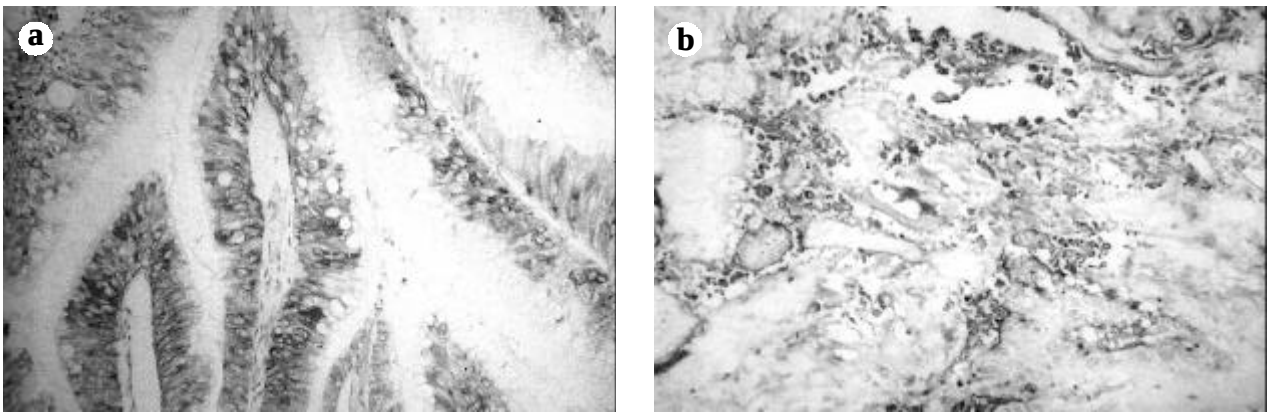

Figure 6. Intraductal papillary-mucinous carcinoma showing positive immunoreactivity for MUC2 a), and a mucinous noncystic carcinoma pattern positive for MUC1 b) (the same case as in Figures. 1 and 2.) X200.

nosis. In this study, 8 IPMCs were immunoreactivity-positive for anti-MUC2 admixing with or without anti-MUC1 immunopositivity in the intraductal component, whereas positivity for anti-MUC1 only, or mixed anti-MUC1 and anti-MUC2 and anti-MUC2 only in the MC pattern were also observed. On the other hand, 3 DAs, including each MC pattern were immunostained positive with anti-MUC1 only, and with mixed anti-MUC1 and anti-MUC2. Hence, the three different MUC immunoreactivities of MCs revealed varying biological reactions between IPMC and DA.

Most previously reported patients with MCs associated with IPMCs had very indolent courses, with death only occurring rarely from the tumor. In this study, however, most patients died within a relatively short period of time. The difference in clinical outcomes between the current study and previous cases cannot be discussed adequately here because of the small number of cases examined. Nevertheless, we distinguished three immunoreacting patterns of MC for anti-MUC1 and anti-MUC2 revealing various characteristics from MUC1 positive DA to MUC2 positive IPMC. Hence, patients with MC may have differences in clinical outcomes.

In conclusion, mucinous noncystic carcinoma is not only a variant of ductal adenocarcinoma, but also an invasive feature of intraductal papillary-mucinous carcinoma. These two pre-existing types of mucinous noncystic carcinoma involved mucin overproduction and mucoid degeneration, respectively. MUC immunoreactivity in mucinous noncystic carcinoma was divided into three categories which may be related to various outcomes.

Acknowledgements

We thank Mr. Hiroshi Abe for his skilful technical assistance and Miss Kaori Kagoshima for typing the manuscript.

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