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Different Clinicopathologic Findings in Two Histologic Types of Carcinoma of Papilla of Vater

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The aim of this study was to investigate the differences between the clinicopathological findings in two histologic types of carcinoma of the papilla of Vater. We histologically classified carcinoma of the papilla into two types: 1) an intestinal type that resembles tubular adenocarcinoma of the stomach or colon, and 2) a pancreaticobiliary type that is characterized by papillary projections with scant fibrous cores. We examined 53 cases of resected carcinoma of the papilla. The intestinal-type carcinomas were similar to the intestinal mucosa in that they had lysozyme-containing, Paneth or argyrophil cells, as demonstrated by the immunohistochemically positive stainings for the anti-lysozyme antibody. Although both the sizes of the two types of carcinomas and the age distributions of cases with the two types of carcinoma were almost the same, the prognosis of the cases with the intestinal type was much better than that of the cases with the pancreaticobiliary type. Histological lymph node metastasis was found significantly more often in the pancreaticobiliary type. This result was supported by the fact that small carcinomas of the intestinal type showed little or no invasion into the surrounding interstitium, as opposed to the pancreaticobiliary type, which had a strong infiltrative tendency. The pathogenesis of carcinoma of the papilla of Vater should be further evaluated, taking into consideration the existence of these two histologic types.

Key words: Intestinal type carcinoma — Pancreaticobiliary type carcinoma — Carcinoma of papilla of Vater

The incidence of carcinoma of the papilla of Vater is increasing in Europe, the United States and Japan.[1)] Due to progress in preoperative patient care, operative mortality in pancreatoduodenectomy has decreased remarkably[1-5)] and the resectability rate of carcinoma of the papilla has been reported to be as high as 79 to 87%.[2-4)] However, the long-term post-operative results are not satisfactory and the 5-year survival rate of pancreatoduodenectomized patients is 21 to 34%.[2-6)] The main reason for this low value is that in most cases, the operation is performed at an advanced stage due to delayed diagnosis.[7-9)] This fact emphasizes the need for early diagnosis.

To obtain an early diagnosis of carcinoma of the papilla of Vater, as well as of carcinomas of other organs, it is extremely important to understand the pathogenesis of the disease. Carcinoma of the papilla has been reported to originate from the epithelia of either the common pancreaticobiliary channel, the bile duct, the pancreatic duct, the duodenal mucosa or the Brunnel glands.[10)] From this viewpoint, we divided the carcinomatous epithelia of the papilla into two groups and clinicopathologically studied cases with carcinoma of the papilla using this classification.

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MATERIALS AND METHODS

We studied 53 cases of carcinoma of the papilla that had been surgically resected between 1965 and 1988 in the First Department of Surgery, University of Tokyo, its affiliated institutions and Tokyo Metropolitan Institute of Gerontology (32 men and 21 women, age 36 to 81 with a mean age of 63.8 years). All of these cases had been resected by a Whipple procedure.

An examination of the gross appearance,[11)] including the determination of the size of the tumor and ulcer formation, was followed by a histological study. The samples were cut into 3 to 5 mm-thick serial sections, which were embedded in paraffin, cut to 4 μm, and stained with hematoxylin and eosin (H & E). These epithelia were examined to determine the two histological types described below. The age, sex, tumor size and prognosis of the each histologic type after surgery were studied. The prognosis was evaluated by the Kaplan-Meier method.

The epithelia of the tumors were histologically divided into two types after H & E stainings: an intestinal type that resembled tubular adenocarcinoma of the stomach or colon (Fig. 1) and a pancreaticobiliary type that was characterized by papillary growth with scant fibrous cores (Fig. 2). With regard to epithelia of intestinal type,

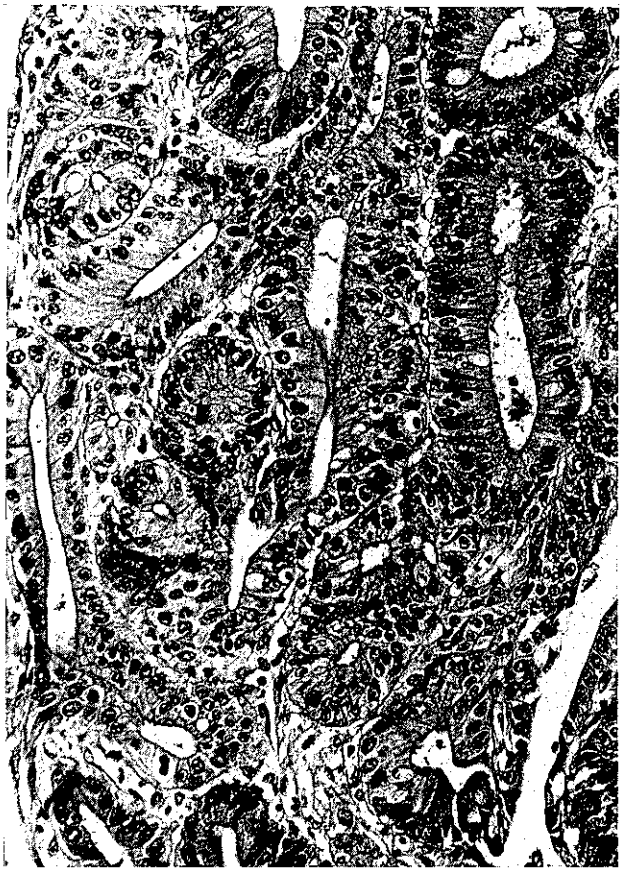

Fig. 1. Epithelium of an intestinal type carcinoma. Irregularly shaped glandular proliferation is massive and stroma is scant. Glandular budding can be observed. Pseudostratification of epithelia is severe (H & E, ×110). Cells are closely arranged, nuclear polarity is considerably lacking, and polymorphism is notable. Large, chromatin-rich nuclei, obviously malignant, are evident.

Fig. 2. A pancreaticobiliary-type epithelium (H & E, ×160). Papillary projections with scant fibrous cores can be observed. Cells are closely arranged, nuclear polarity is absent and polymorphism is notable. Large, chromatin-rich nuclei, obviously malignant, are evident.

differentiation (well, moderate or severe) was further studied.

We also studied the epithelia of the tumors immunohistochemically and histochemically. To investigate intestinal metaplasia, deparaffinized sections were examined by the peroxidase-antiperoxidase (PAP) immunohistochemical technique with anti-lysozyme antibody (Takeda, Tokyo). Samples were also examined histochemically with Grimelius stainings. Paneth cells were also studied in the H & E stainings.

RESULTS

The pancreaticobiliary and intestinal histologic types of carcinoma of the papilla of Vater were found in 38 (72%) and 13 (25%) cases, respectively. Among these 51 cases, the concomitant presence of both types of epithelia was found in eleven cases (seven cases: pancreaticobiliary type, four cases: intestinal type). However, the percent area of the predominant histologic type was more than 70% in three cases and more than 90% in the other eight cases. Therefore, we classified these eleven cases according to the predominant histological type of epithelia. Undifferentiated carcinoma was found in 2 cases (4%). Paneth cells, argyrophil cells (Fig. 3) and cells that were positively stained for the anti-lysozyme antibody (Fig. 4) were found more often in the intestinal type than in the pancreaticobiliary type (Table I). The differentiation of intestinal type of epithelia was well-differentiated in ten cases and moderate in three cases.

The male-female ratio was almost 2:1 in the pancreaticobiliary type and 1:1 in the intestinal type. Cases of the two types had almost the same mean age (Table

II). The age distributions of patients with the two types of carcinoma were almost the same (Table III).

The distribution of tumor size was almost the same in both types of cases (Table IV). However, the incidence of histological lymph node metastasis was significantly higher in cases of the pancreaticobiliary type than in those of the intestinal type. The incidences of both gross ulceration and histological infiltration of pancreatic parenchyma were also more frequent in the pancreaticobiliary type than in the intestinal type, but these differences were not statistically significant.

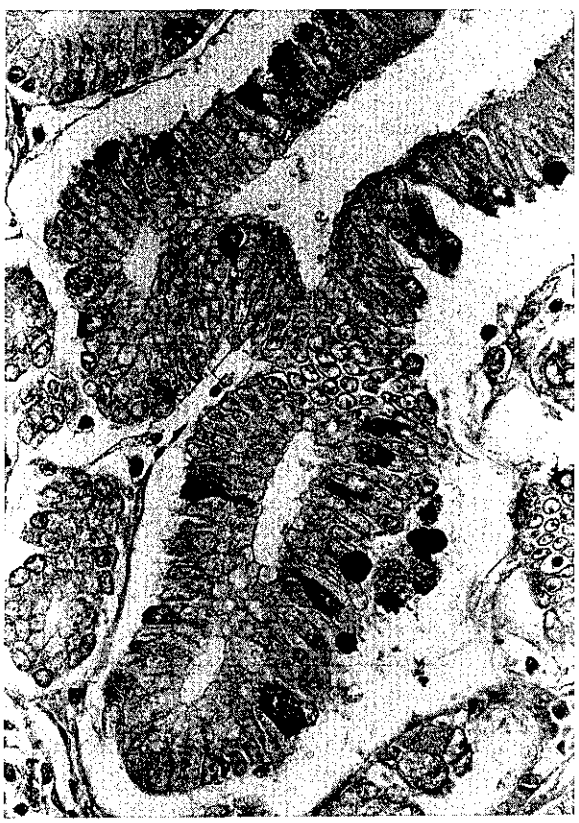

Fig. 3. Argyrophil cells of epithelium of the intestinal type, positive for Grimelius staining (×210).

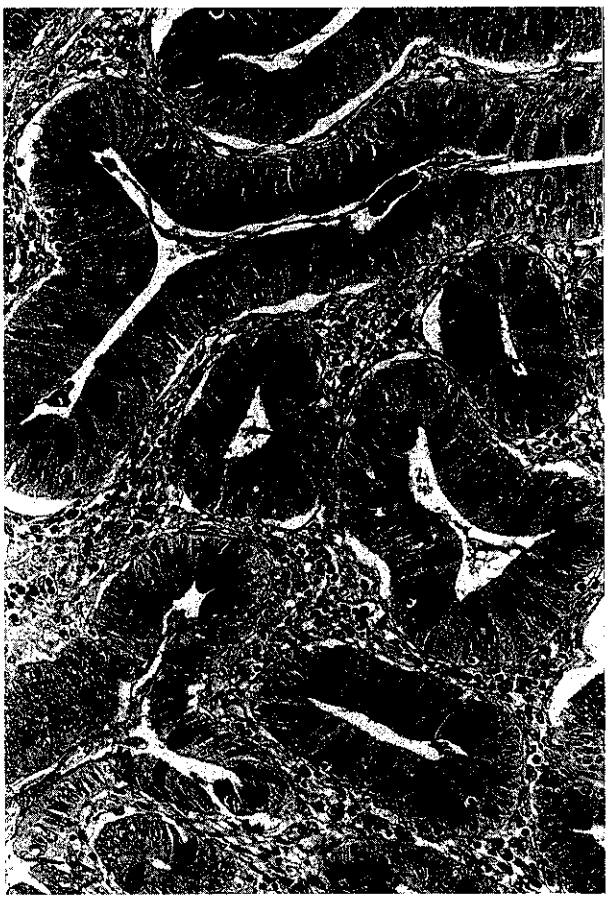

Fig. 4. Immunohistochemical reaction of anti-lysozyme antibody. Many cells were positively stained, with an intense reaction (×210).

Table I. Incidence of Paneth Cells, Argyrophil Cells and Cells Positive for Antilysozyme Antibody in Cases of Pancreaticobiliary or Intestinal Type of Carcinoma of the Papilla of Vater (%)

	Paneth cells		Argyrophil cells		Lysozyme-containing cells	
Carcinoma of the pancreaticobiliary type	0/38 (0)	*	0/12 (0)	NS	3/12 (25.0)	NS
Carcinoma of the intestinal type	5/13 (38.5)		1/5 (20.0)		4/5 (80.0)	
Undifferentiated carcinoma	0/2 (0)		0/1 (0)		0/1 (0)	

* Fisher's exact test; $P<0.01$. NS, not significant.

Table II. Male/Female Ratio and Mean Age of Cases of Pancreaticobiliary or Intestinal Type of Carcinoma of the Papilla of Vater (%)

	Cases with pancreaticobiliary type carcinoma	Cases with intestinal type carcinoma	Cases with undifferentiated carcinoma	Total
Male/female	25:13	6:7	1:1	32:21
Mean age	62.8	64.5	78.0	63.8

Table III. Age Distribution of Cases with Various Types of Cancerous Epithelia of the Papilla of Vater

Age	Cases with pancreaticobiliary type carcinoma	Cases with intestinal type carcinoma	Cases with undifferentiated carcinoma	Total
30–39	1 (2.6)	0	0	1
40–49	3 (7.9)	2 (15.4)	0	5
50–59	13 (34.2)	1 (7.7)	0	14
60–69	8 (21.0)	5 (38.5)	0	13
70–79	12 (31.6)	4 (30.8)	2 (100)	18
80–89	1 (2.6)	1 (7.7)	0	2
Total	38 (71.7)	13 (24.5)	2 (3.8)	53

Table IV. Tumor Size, Ulcer Formation, Histologic Pancreatic Infiltration and Lymph Node Metastasis in Cases with Carcinoma of Pancreaticobiliary Type or Intestinal Type of the Papilla of Vater (%)

	Histologic type of the epithelium	
	Pancreaticobiliary type (n=38)	Intestinal type (n=13)
Tumor size (cm)		
0–1.0	3 (7.9)	2 (15.4)
1.1–1.5	5 (13.1)	1 (7.7)
1.6–2.0	9 (23.7)	5 (38.5)
2.1–3.0	12 (31.6)	3 (23.1)
3.1–4.0	6 (15.8)	2 (15.4)
4.1–	3 (7.9)	0
Ulcer formation	NS	
	20/38 (52.6)	3/13 (23.1)
Histologic pancreas invasion	NS	
	21/38 (55.3)	4/13 (30.8)
Histologic lymph node metastasis	*	
	21/38 (55.3)	2/13 (18.2)

* Fisher's exact test; $P<0.05$. NS, not significant.

Very small carcinomas, less than 1.5 cm in diameter, were found in eight cases of the pancreaticobiliary type and in three cases of the intestinal type. Massive invasion of the parenchyma was found in the pancreaticobiliary type. In contrast, carcinoma of the intestinal type showed little or no invasion.

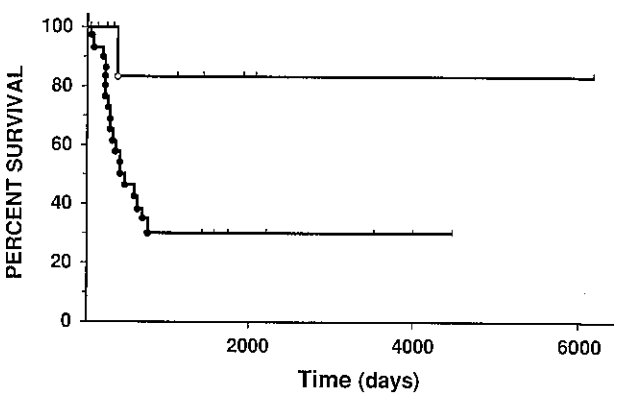

Fig. 5. Survival curves of the cases with either intestinal (○) or pancreaticobiliary (●) type of carcinoma of the papilla of Vater (Kaplan-Meier method; $P<0.01$).

Survival curves for both types of cacinoma are shown in Fig. 5. Long-term survival after resection of the tumor was significantly greater in the cases with intestinal type than in those with the pancreaticobiliary type.

DISCUSSION

Carcinoma of the papilla has traditionally been classified into papillary type and non-papillary type.[3,7-9] However, recent findings have suggested that this classifica-

tion is inadequate. Neoptolemos *et al.*[12] reported that this classification does not clearly express the relationship between the histologic types and the degree of invasion of the cancer. In addition, some reports[8,9] have used the terms "papillary type" and "non-papillary type" as synonyms for "noninvasive carcinoma" and "invasive carcinoma," respectively.

In this study, we divided carcinomatous epithelia of the papilla into two types: an intestinal type and a pancreaticobiliary type. This classification was based on the possible sites of development of carcinoma in this region reported by Outerbridge.[10] The epithelia of the intestinal type resemble those of tubular adenocarcinoma of the colon or stomach. These epithelia may originate from the duodenal mucosa. On the other hand, epithelia of the pancreaticobiliary type may originate from pancreaticobiliary epithelia, since the epithlium of the pancreatic or bile duct often shows papillary growth with a scant fibrous core.[13,14] The prevalence of the intestinal type was 25%, which was much less than that of the pancreaticobiliary type. This result agreed with our previous report[15] which showed that most cases of carinoma of the papilla of Vater originate from the epithelia of the pancreaticobiliary channel in the papilla and not often from the duodenal mucosa.

In the present study, we found a clear difference between the two histologic types from the standpoint of the intestinal metaplasia. Paneth and argyrophil cells were found only in the intestinal type. The epithelia of this type were more frequently positive for anti-lysozyme antibody. Paneth cells and argyrophil cells are usually found in the intestinal epithelium.[16] Lysozyme has also been reported in the intestinal mucosa.[16] These cells have also been found in the carcinoma of the stomach and colon. Our results show that classification of the two histologic types of tumor of the papilla based on hematoxylin-eosin stainings is supported by these other histologic, histochemical and immunohistochemical parameters.

The tumor size was evenly distributed in both types of carcinoma. However, histological lymph node metastasis was much more frequent in the pancreaticobiliary type than in the intestinal type. Furthermore, the prognosis was much worse in the pancreaticobiliary type. The pancreaticobiliary type also showed a strong tendency to invade the interstitium, even if the tumor was very small. These results correspond to the report by Neoptolemos *et al.*[12] that intestinal-type tumors are less aggressive. On the other hand, these results contradict reports based on the traditional classification which claim that papillary-type carcinomas convalesce more satisfactorily.[3,7-9] However, when we carefully examine these reports, the criteria used to make the classification seem to be considerably different from those we used in the present study. For example, Fig. 3 (top right) in the report by Akwari *et al.*[3] claims to depict the papillary type, although we would classify this particular example as intestinal type.

It is noteworthy that most of the carcinomas with intestinal-type epithelia were well differentiated. The better prognosis of this type may be due to this fact. Nevertheless, we believe that the results of the present study indicate that these two types carcinoma should be treated by different operative procedures or adjuvant therapies. When the carcinoma is shown to be of the intestinal type, advanced lymph node dissection may not be necessary. However, complete and thorough lymph node dissection during surgery and intensive adjuvant therapy, such as chemotherapy or radiation, may be required in cases of the pancreaticobiliary type of carcinoma of the papilla of Vater.

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