

The Role of Bile Carcinoembryonic Antigen in Diagnosing Bile Duct Cancer

It is known that the fluids bathing tumors might contain a higher level of the carcinoembryonic antigen (CEA) than those found in the blood. Therefore, we evaluated the role of bile CEA in diagnosing bile duct cancer. One hundred and thirty two patients were prospectively studied. The patients were divided into 3 groups: the bile duct cancer (n=32), pancreatic cancer (n=16), and benign biliary diseases (n=84) groups. Bile samples were obtained on the next day of the biliary drainage procedures. The mean bile CEA level in those with bile duct cancer (120.6 ± 156.9 ng/mL) was significantly higher than those with pancreatic cancer and benign biliary diseases (32.0 ± 28.5 ng/mL, 29.3 ± 56.3 ng/mL). Using the level of 20 ng/mL, the sensitivity and specificity of bile CEA in the diagnosis of bile duct cancer from benign biliary diseases were 65.6% and 66.7%, respectively. Both the bile CEA and total bilirubin level were found to be an independent factor linked to bile duct cancer. This study result suggests that bile CEA level is a useful supplementary test for diagnosing bile duct cancer.

Key Words : *Carcinoembryonic Antigen; Bile; Bile Duct Neoplasms*

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INTRODUCTION

The carcinoembryonic antigen (CEA), first described by Gold and Freedman in 1965, is a highly glycosylated cell surface glycoprotein with a molecular weight of 180,000, which is believed to be an oncofetal protein specific for the colon (1). The potential use of a circulating tumor marker includes screening the populations at risk of developing a tumor, making an unequivocal diagnosis of the presence of a tumor, determining the prognosis, assessing the therapeutic efficacy, and detecting residual or recurrent cancer. Currently, the performance of the available tumor markers as screening tests for diagnosing a malignancy in high risk individuals is inadequate because of the reduced sensitivity and occasional false-positive results (1-3). However, several studies have suggested that measuring the CEA in the body fluid bathing primary or metastatic tumors may be more useful than the serum value (4-14). The aim of this study was to determine the diagnostic role of the bile CEA levels in patients with bile duct cancer.

MATERIALS AND METHODS

The study included 132 patients with biliary tract diseases or pancreatic head cancer with a bile duct invasion from November 2001 to May 2003, who had undergone an endo-

scopic biliary drainage or a percutaneous transhepatic biliary drainage as a result of a biliary obstruction with/without cholangitis. The exclusion criteria were an associated other site tumor that may have influenced the bile CEA levels, some biliary tract malignancies such as gallbladder or ampulla of Vater cancer, pancreatic body or tail cancer, and bile obtained directly from the gallbladder. Serum samples were taken from all the patients immediately before the biliary drainage procedures and bile samples were obtained from the drainage catheter on the next day of the biliary drainage procedures in order to exclude dilution effects of the previous injected dyes. The bile CEA levels were determined with a two-site sandwich immunoassay using a direct chemiluminometric technique (ADVIA Centaur CEA assay, Bayer, East Walpole, MA, U.S.A.).

The patients' age ranged from 25 to 91 yr (mean 63.0 ± 13.2), and the male to female ratio was 77:55. All the patients were divided into 3 groups: the bile duct cancer (n=32), the pancreatic cancer (n=16), and the benign biliary diseases (n=84) groups (Table 1). The benign biliary diseases consisted of 62 common bile duct stones, 6 intrahepatic duct stones, 10 both intra and extrahepatic duct stones, 6 benign bile duct strictures with/without stones. Both bile duct and pancreatic cancer were diagnosed by the radiographic studies or pathological findings of the biopsy specimens and/or by the operative findings with/without pathological examination of resected tumors. Statistical analysis was performed

by a one-way analysis of variance (ANOVA) to analyze the differences in the variables including the bile CEA level among the groups, and by logistic regression to evaluate the diagnostic value of the bile CEA level. The results are expressed as a mean \pm standard deviation of the mean. A p value <0.05 was considered significant. Statistical analysis was done using the SPSS/PC+ version 9.0 software.

RESULTS

The distribution of the bile CEA levels among the groups is shown in Fig. 1. The mean bile CEA in the bile duct cancer group was 120.6 ± 156.9 ng/mL, 32.0 ± 28.5 ng/mL in the pancreatic cancer group, and 29.3 ± 56.3 ng/mL in the benign biliary diseases group. The mean bile CEA level in the bile duct cancer patients was significantly higher than in the pancreatic cancer and benign biliary diseases patients ($p < 0.05$). On the other hand, the mean bile CEA level in the pancreatic cancer patients was not statistically different from that in the benign biliary diseases patients. As the normal value of bile CEA was not known, we had to determine the receiver operating characteristic (ROC) curves. Therefore, a value of 20 ng/mL was chosen to significantly improve the specificity, without reducing the sensitivity. Using a cut-off level of 20 ng/mL, the sensitivity and specificity of the bile CEA in detecting bile duct cancer was 65.6% and 66.7%, respectively. In addition to the bile CEA levels, the total bilirubin and alkaline phosphatase level were also found to be significantly different among the groups (Table 1). To determine whether or not the bile CEA levels were related

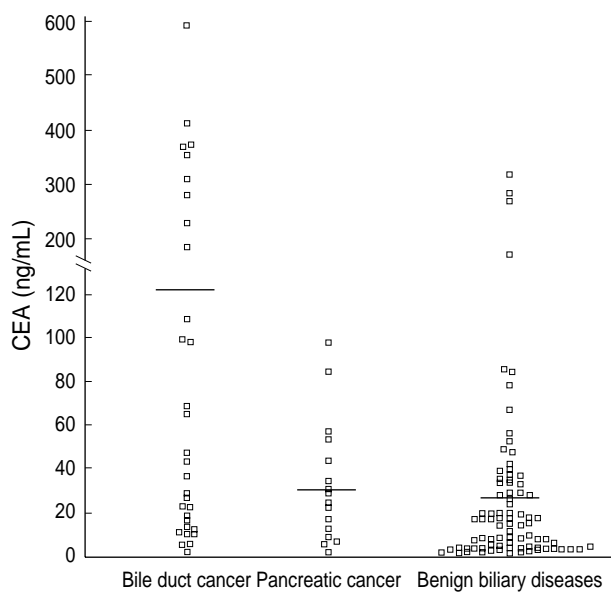


Fig. 1 Distribution of the bile CEA levels according to the groups. The level of CEA in patients with bile duct cancer is significantly different in comparison with those in patients with pancreatic cancer and benign biliary diseases. Bars are expressed as mean.

to a biliary obstruction, the bile CEA levels were compared with a liver function test. The bile CEA did not correlate with either the bilirubin or alkaline phosphatase levels (Table 2). Among the variables, the bile CEA, total bilirubin, alkaline phosphatase, and γ GT levels directly correlated with a malignancy in biliary tract diseases including bile duct cancer and benign biliary diseases. In particular, both the bile CEA and total bilirubin level were found to be an independent factor linked to bile duct cancer ($p < 0.05$).

DISCUSSION

CEA is a 180,000 Da glycoprotein that is often found in patients with malignant tumors of the digestive system (1, 2). This antigen has been detected in various body fluids such as the gastrointestinal and pancreatobiliary juice (4-14). Several studies have described the diagnostic utility of the increased CEA levels in the body fluids in primary malignant tumors arising from the stomach, colon, biliary tract, and pancreas (4-11). In particular, some attempts have been made to analyze the bile juice for a measurement of the CEA content to predict the presence of bile duct cancer (7-11). In addition to a primary malignant tumor, the relationships

Table 1. Comparative data* among the groups

	Bile duct cancer	Pancreatic cancer	Benign biliary diseases
No.	32	16	84
Age (yr)	62.8 ± 11.8	67.8 ± 10.5	62.1 ± 14.1
Male (%)	69	69	52
WBC ($\times 10^3/\mu\text{L}$)	9.0 ± 3.5	8.7 ± 4.5	8.6 ± 4.1
Bile CEA (ng/mL) [†]	120.6 ± 156.9	32.0 ± 28.5	29.3 ± 56.3
Bilirubin (mg/dL) [†]	7.7 ± 5.8	7.1 ± 5.9	3.0 ± 5.0
AST (IU/L)	116.6 ± 125.6	166.9 ± 160.2	147.6 ± 194.7
ALT (IU/L)	152.5 ± 157.5	229.1 ± 194.3	156.9 ± 170.6
ALP (IU/L) [†]	375.5 ± 266.0	421.5 ± 226.3	237.4 ± 196.1
γ GT (IU/L)	576.2 ± 512.2	605.3 ± 408.2	394.8 ± 369.1
CS (%)	44	23	29

*Values of data are the mean \pm SD except for male sex ratio and *Clonorchis sinensis* infection rate. [†]Significantly different at $p < 0.05$ between bile duct cancer and benign biliary diseases. CS, *Clonorchis sinensis* infection rate.

Table 2. Correlation between biliary CEA and liver function test

	bCEA	BIL	AST	ALT	ALP	γ GT
bCEA	1					
BIL	.058	1				
AST	.034	-.013	1			
ALT	-.004	.067	.825 [†]	1		
ALP	.060	.338 [†]	.162	.194 [*]	1	
γ GT	.097	.184 [*]	.222 [*]	.349 [†]	.647 [†]	1

* $p < 0.05$. [†] $p < 0.01$.

bCEA, biliary CEA; BIL, total bilirubin; ALP, alkaline phosphatase.

between the bile CEA levels in the gallbladder or bile duct and a colorectal liver metastasis have been also reported (12-14). These attempts to determine the CEA level in the body fluids may be attributed to the notion that the fluids bathing the tumors in the primary or metastatic sites might contain higher CEA levels than those found in the blood pool. Unfortunately, several reports have shown nonspecific elevations of the bile CEA levels in benign biliary diseases patients, e.g. choledocholithiasis (8-11, 15).

In contrary to the bile CEA levels, the serum CEA level may be controlled by several factors, including the production of CEA by cancer cells, the release from the tumor directly into the blood stream and its metabolic degradation in the liver (16, 17). However, the body fluids including bile, cystic fluids, and gastrointestinal juice, are in close contact with or contain the tumors, so they have a large quantity of CEA discharged from the tumor itself. Moreover, this considerable portion is not exposed to the degradation process in the liver (18). In addition, the elevated CEA levels in body fluids become rapidly detectable because their volume is much smaller than the blood volume (19). Therefore, a CEA assay of the fluids bathing a tumor may be a more reliable system as an aid in diagnosis than that in the serum. In this respect, this study focused on whether or not the bile CEA level would be a useful tool for diagnosing bile duct cancer. In particular, as the bile obtained from the bile duct is directly in contact with bile duct cancer and is not affected by either the gallbladder function or the cystic duct patency (7). Therefore, it is expected that a hepatic bile CEA assessment would be more useful in diagnosing bile duct cancer, compared to gallbladder or pancreatic cancer. These results showed that the bile CEA level in bile duct cancer patients was significantly higher than that in benign biliary diseases patients. Furthermore, logistic regression analysis of the variables showed that the bile CEA level in addition to the total bilirubin level are independent variables linked to bile duct cancer. It is suggested that the bile CEA level may to some extent be a useful supplementary tool in distinguishing bile duct cancer from benign biliary diseases, particularly in an equivocal situation, which is unjustly suspected of bile duct cancer. However, the bile CEA level in pancreatic cancer patients was not only lower than that in bile duct cancer patients, but there was also no difference from that in the benign biliary diseases patients. This may be partly caused by the anatomical separation between the common bile duct and the pancreatic tumor despite the biliary obstruction by the tumor.

As mentioned above, several studies have indicated that nonspecific elevations of the bile CEA levels were observed in patients with benign biliary diseases (8-11, 15). This phenomenon may be explained by the fact that human bile contains several CEA related substances such as biliary glycoprotein 1, a nonspecific cross-reacting antigen that can potentially cross-react with CEA (10). Hence, the values for the CEA levels in the bile may be influenced by the presence of

CEA related substances. To overcome this problem, a recent study performed immunochemical analysis for a specific CEA investigation, and observed that CEA was found only in those patients with bile duct cancer whereas only CEA related-substances were found in benign biliary diseases patients. This suggests that the Western blot analysis of bile CEA can differentiate CEA from CEA related substances and be helpful for detecting the presence of a tumor (10). Unfortunately, this study did not perform the Western blot analysis of bile CEA. Nevertheless, it is obvious that in some bile duct cancers, the bile CEA level will be significantly higher than in benign biliary diseases patients.

In conclusion, bile CEA appears to have a limited use in screening for bile duct cancer because of its low sensitivity and specificity. However, in some situations, particularly when the diagnosis remains obscure, the bile CEA level may be applied as a useful supplementary test in making a distinction between malignant and benign biliary diseases.

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