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Are serum and biliary carcinoembryonic antigen and carbohydrate antigenl9-9 determinations reliable for differentiation between benign and malignant biliary disease?

Malign ve benign safra yollan hastalıklarının ayırıcı tanısında serum ve safra karsinoembriyotik antigen, karbohidrat antiegen19-9 düzeyi güvenilir mi?

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Background!aims: *The value of serum tumor markers carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) in the differential diagnosis of obstructive biliary disease is dubious. We aimed to define their usefulness prospectively.* ***Methods:*** *Thirty-seven consecutive patients (12 female, 25 male, median age: 54, range: 19-83 years) who were referred for endoscopic retrograde cholanugiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) examination for obstructive jaundice were included (all with dilatation of biliary tree in ultrasonography or computerised tomography). Bile was obtained through the nasobiliary or external drainage catheter, placed with ERCP or PTC, respectively. Serum samples were taken from all patients at the time of acquisition of bile. Serum and bile samples were stored at -50 °C until they were tested. CA19-9 and CEA levels were measured with chemiluminescent enzyme immunoassay methods in serum and bile samples by using immulite GI-MA and CEA commercial kits, respectively (DPC®, Los Angeles).* ***Results:*** *In 22 patients with malignant disease, serum CEA levels were 38.6± 115.8 ng/ml and CA19-9 were 386.9±409.7 U/ml, while in 15patients with benign disease the serum CEA levels were 1.8±1.6 ng/ml and CA19-9 were 128.9±302.2 U/ml. The difference for both values was significant (p<0.05). In malignant disease bile CEA and CA19-9 levels were 160.8±457.8 ng/ml, 14000.9±19798 U/ml respectively, while in benign disease the corresponding levels were 21.08±48.6 ng/ml for CEA and 14818.9±24665.7 U/ml for CA19-9. The differences were not significant in this case (p>0.05).* ***Conclusion:*** *It was concluded that serum CA19-9 levels are increased both in malignant and benign obstructive biliary diseases, albeit more significantly in the former. However, increase in serum CEA is mostly restricted to malignant diseases. Measurement of these markers in bile is of no value.*

Keywords: Carcinoembryonic antigen, carbohydrate antigen, CA19-9, hepatopancreatobiliary disease, bile

Amaç: *Benign ve malign safra yolları hastalıklarının ayırıcı tanısında serum CEA ve CA19-9 düzeyinin rolü tartışmalıdır. Prospektifolarak dizayn edilmiş bu çalışmada, kullanabilirliklerini araştırdık.* ***Yöntem:*** *Çalışmaya Ağustos 1999- Nisan 2000 tarihleri arasında ERCP laboratuvarına veya servisimize tıkanma sarılığı nedeniyle başvuran 37 (12 Kadın, 25 Erkek, ortanca yaş; 54 sınırlar; 19-83) hasta alındı. Safra PTK yoluyla yerleştirilen eksternal katater veya ERCP ile yerleştirilen NBD yoluyla elde edildi. Serum örnekleri, safra örneklerinin alımı ile eş zamanlı alındı. Serum ve safra örnekleri, çalışma anma kadar -50 C°de bekletildi. CA19-9 düzeyi immulite GI-MA, CEA immulite CEA (DPC®, Los Angeles) ticari kiti kullanılarak, semilüminisent enzim immunassay yöntemiyle çalışıldı.* ***Bulgular:*** *Yirmiiki malign hastalıkta serum CEA:38.6±115.8 ng/ml, CA19-9: 386.9±409.7 U/ml iken benign nedenlere bağlı tıkanma sarılığı olan 15 olguda bu oran sırasıyla 1.8±1.6 ng/ml, 128.9±302.2 U/ml olarak bulundu. Serum CEA ve CA19-9 düzeyi malign hastalıklarda anlamlı olarak daha yüksekti (p<0.05). Aynı olguların safra değerleri ise malign olgularda CEA: 160.8±457.8 ng/ml, CA19-9: 14000.9±19,798U/ml, benign olgularda CEA: 21.08±48.6 ng/ml, CA19 9: 14818.9±24665.7 U/ml olarak bulundu ve her iki grup arasında istatistiksel anlamlılık yoktu (p>0.05).* ***Sonuç:*** *Sonuç olarak malign ve benign safra yolları hastalıkların ayırıcı tanısında serum CEA, CA19-9 düzeyinin tayini anlamlıyken, safra da her iki tümör antijeninin tayini güvenilir olmayan işaretleyiciler olarak değerlendirildi.*

Anahtar kelimeler: Karsinoembriyonik antijen, karbohidrat antiegen19-9, hepatopankreatikobilier hastalık, safra

INTRODUCTION

Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) are tumor markers for the diagnosis of gastrointestinal cancers. However, their serum levels have been found elevated in some benign diseases, such as pancreatitis, cholangitis, hepatitis and cirrhosis, as well (1-3). Their use in the differential diagnosis is not well defined.

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Both CEA and CA19-9 are produced by epithelia of the pancreas, stomach, colon, liver, and biliary tract. Small tumors produce detectable levels of the CEA or CA19-9 antigen only in the body fluids such as bile, and this was suggested as a useful tool in the patient with otherwise occult liver metastasis (4, 5) or with primary tumors (6). Our aim was to determine serum and bile CA19-9 and CEA levels in the differential diagnosis of benign and malignant hepatopancreatobiliary diseases.

MATERIALS AND METHODS

Between November 1999-August 2000, 37 consecutive patients (12 female, 25 male, median age: 54 yr, range: 19-81) with diagnosis of obstructive jaundice were studied. (The diagnosis was based on ultrasonography (US) and/or computerised tomography (CT) findings). Endoscopic retrograde cholangio-pancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) was performed. Bile was obtained through the nasobiliary or external drainage catheter, placed with ERCP or PTC, respectively. Serum samples were taken from all patients for CEA and CA19-9 at the time of acquisition of bile. Serum and bile samples were stored at -50 °C until they were tested. Bile samples were mixed with 0.1 M acetic acid at 70 °C for 15 minutes followed by centrifugation for 10 minutes at 3000g for the elimination of bile pigments and other proteins before the measurements (7). All CEA and CA19-9 bile samples were tested after dilution at titers of 1/10, 1/20 and 1/40 or 1/40, 1/80 and 1/160, if required. The distinction between malignant and benign was based on clinical or radiological findings (US and/or CT, ERCP or PTC). The diagnosis of primary sclerosing cholangitis (PSC) was based on compatible cholangiographic features, biochemical and clinical findings, and exclusion of PSC-like diseases. Histology was available in one-fourth of the patients as well. Alkaline phosphates, GGT, ALT, AST, total bilirubin levels and white blood cell (WBC) count were studied in all patients. CA19-9 and CEA levels were measured with chemiluminescent enzyme immunoassay methods in serum and bile samples by using immulite GI-MA and CEA commercial kits, respectively (DPC®, Los Angeles).

Serum upper limit of normal for CA19-9 was 37 ng/ml and for CEA was 5 ng/dl. Normal levels are undefined for bile samples.

This study was approved by the ethical committee of our hospital and strictly adhered to the Helsinki Declaration.

Mann-Whitney U and Pearson Moment Correlation tests were used for statistical analysis, and a p value less than 0.05 was considered statistically significant.

RESULTS

Twenty-two patients with malignant disease and 15 patients with benign disease were studied. Median age was 54 years. The etiology of malignant disease was cholangiocarcinoma in 15, papillary carcinoma in 2, pancreatic head carcinoma in 2, metastatic carcinoma in 2 (1 stomach, 1 colon), and gallbladder carcinoma in 1. Mean serum CEA level in the malignant group was 38.6±115.8 ng/ml while bile CEA level was 160.8 ± 457.8 ng/ml. The concentration of serum and bile CA19-9 levels in these groups was 386 ± 409.7 U/ml and 14000.9 ± 19798 U/ml, respectively. The benign diseases were hydatic disease related biliary stricture in 4, choledochal stone and cholangitis in 4, primary sclerosing cholangitis in 4, Caroli's disease in 1 and cholangitis due to fasciola hepatica in 1. Mean serum CEA value in benign disease was 1.8 ± 1.6 ng/ml while CA19-9 was 128.9 ± 302.2 U/ml.

The mean serum CEA for the malignant group (38.6±115.8 ng/ml) was significantly higher than for the benign group (1.8 ± 1.6 ng/ml) (p=0.001). While 6 of 21 (29%) patients with malignant disease had serum CA19-9 levels exceeding 1000 ng/ml, such a high value was detected in only 1 of 37 (2.7%) patients with benign disease. Serum CA19-9 concentration was significantly higher in patients with malignant disease (386 ± 409.7 U/ml) in comparison to patients with benign diseases (128.9 ± 302.2 U/ml) (p=0.002).

In benign group, mean bile CEA and CA19-9 levels were 21.08 ± 48.6 ng/ml, 14818.9 ± 24665.7 U/ml, respectively. Biliary CA19-9 levels in patients with malignant diseases were not significantly different from those in the patients with benign disease (p>0.05). As expected, bile levels for both markers were higher than their corresponding serum levels. We did not find any significant correlation between the serum levels of CA19-9 or CEA and WBC count. Furthermore, no correlation was observed between the presence of cholangitis and the values of these tumor markers (p>0.05). Results are shown in (Table 1).

Table 1. The bile and serum levels of CEA and CA19-9 in benign and malignant pancreato-biliary diseases.

Parameters	Malignant Disease n=22	Benign Disease n=15	P
Serum CEA levels (ng/ml)	38.6±115.8	1.8±1.6	0.001
Serum CA19-9 levels (U/ml)	386.9±409.7	128.9±302.2	0.002
Bile CEA levels (ng/ml)	160.8±457.8	21.08±48.6	0.2
Bile CA19-9 levels (U/ml)	14000.9±19798	14818.9±24665.7	0.8

DISCUSSION

In our study, serum CEA and CA19-9 levels were found to be elevated in patients with malignant biliary diseases. The levels of CEA or CA19-9 in the bile of patients, both with and without malignancy, were high and widely distributed. Biliary CEA levels in patients with malignant diseases tended to be higher when compared to benign group; however, both markers' bile levels failed to discriminate between benign and malignant disease. Furthermore, bile levels have a poor discriminatory value in comparison with serum levels.

CEA and CA19-9 may help in the detection of early tumor and determination of tumor stage, prognosis and recurrence. Unfortunately, no tumor markers are accurate enough to provide reliable information about tumor diagnosis and prognosis (8-10). Serum CA19-9 level, in particular, can be elevated in some benign conditions such as cholangitis and biliary obstruction, which can cause confusion when it is used as a diagnostic test for gastrointestinal malignancy (1,2). We observed that some patients with benign disease had an elevated level of serum CA19-9 and CEA; however, these levels in the malignant group were markedly higher. Six (29%) of 22 patients with malignant disease had exhibited CA19-9 levels >1000U/ml in contrast with only two (5.4%) patients presenting with benign disease.

The differentiation of cholangiocarcinoma from benign biliary tract stricture and detection of early metastasis of the colon and pancreas cancers remain quite challenging. Ultrasonography and CT scanning are useful means of demonstrating dilated intrahepatic biliary ducts and/or masses; however, none of these imaging techniques is very sensitive in the detection of early tumors and metastasis (11). In view of the difficulty in establishing the diagnosis of cholangiocarcinoma (6) and in detection of colorectal (4, 12, 13) and pancreas cancers (5) metastatic to the liver, several studies have suggested that bile levels of CEA and CA19-9 should be measured. Their levels have been found to be elevated in the bile of patients with liver metastasis and pancreatico-biliary cancers (5,14,15). However, the results concerning their diagnostic value in differentiating between malignant and benign disease (16,17) and identifying patients with occult liver metastasis (18) are conflicting. Measurement of serial bile and serum CEA or CA19-9 levels have been found to be useful to determine the development of cholangiocarcinoma in the follow-up of premalignant biliary diseases such as PSC, choledochal cyst, and intrahepatic stones (6). Measurament of these markers in bile periodically after resection of primxy tumor was also recomuended (5, 12).

An obstruction of bile flow from any cause can lead to an increase in the bile levels of CEA or CA19-9 and leak out into the bloodstream (1, 2). One limitation of our study can be only single determination of these markers. The measurement of serial serum and bile levels after relief of obstruction may be of advantage in order to decrease the influence of cholestasis on the CEA and CA19-9 levels (1, 2). Nevertheless it has been reported that removal of the obstruction of the biliary tract in patients with carcinoma did not result in a marked decrease of the marker bile levels. The authors suggested that CEA or CA19-9 levels in the bile were more influenced by marker production by the cancer than by the hepatobiliary factors (1,15). In our study, no difference was found in the levels of these tumor markers in the bile between patients with and without cholangitis. Their biliary levels were similar in patients with malignant and benign disease as well. It has also been reported that the measurement of these antigens in bile seemed to be of little diagnostic value in the differentiation between malignant and benign diseases (17, 19).

In conclusion, serum CA19-9 levels are increased both in malignant and benign obstructive biliary diseases, albeit more significantly in the former. However, an increase in serum CEA is mostly restricted to malignant diseases. Measurement of these markers in the bile appears to be of no value.

Further prospective studies are warranted to assess the real value of tumor markers for the differential diagnosis between the two groups.

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REFERENCES

1. Mann DV, Edwards R, Ho S, et al. Elevated tumor marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol 2000; 26: 474-9.
2. Akdoğan M, Sasmaz N, Kayhan B, et al. Extraordinarily elevated CA19-9 in benign conditions: a case report and review of the literature. Tumori 2001; 87: 337-9.
3. Giannini E, Borro P, Botta F, et al. Cholestasis is the main determinant of abnormal CA19-9 levels in patients with liver cirrhosis. Int J Biol Markers 2000; 15: 226-30.
4. Yeatman TJ, Bland Ki, Copeland EM, et al. Relationship between colorectal liver metastases and CEA levels in gallbladder bile. Ann Surg 1989; 210: 505-12.
5. Montgomery RC, Hoffman JP, Ross E A, et al. Biliary CA19-9 values correlate with the risk of hepatic metastases in patients with adenocarcinoma of the pancreas. J Gastrointest Surg 1998; 2: 28-35.
6. Nakeeb A, Lipsett PA, Lillemoe KD, et al. Biliary carcinoembryonic antigen levels are a marker for cholangiocarcinoma. Am J Surg 1996; 171: 147-53.
7. Maiolini R, Bagrel A, Chavance C, et al. Study of an enzyme immunoassay kit for carcinoembryonic antigen. Clin Chem 1980; 26: 1718-22.
8. Kim HJ, Kim MH, Myung SJ, et al. A new strategy for the application of CA19-9 in the differentiation of pancreatobiliary cancer: analysis using receiver operating characteristic curve. Am J Gastroenterol 1999; 94: 1941-6.
9. Bjornsson E, Kilander A, Olsson R. CA19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. Liver 1999; 19: 501-8.
10. Ramage JK, Donaghy A, Farrant M, et al. Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology 1995; 108: 865-9.
11. Campbell WL, Ferris JV, Holbert BL, et al. Biliary tract carcinoma complicating primary sclerosing cholangitis: evaluation with CT, cholangiography, US, and MR imaging. Radiology 1989; 207: 41-50.
12. Paul MA, Visser JJ, Mulder C, et al. The use of biliary CEA measurements in the diagnosis of colorectal cancer. Eur J Surg Oncol 1997; 23: 419-23.
13. Ishida H, Yoshinaga K, Gonda T, et al. Biliary carcinoembryonic antigen levels can predict metachronous liver metastasis of colorectal cancer. Anticancer Res 2000; 20: 523-6.
14. Brockmann J, Emparan C, Hernandez CA, et al. Gallbladder bile tumor marker quantification for detection of pancreato-biliary malignancies. Anticancer Res 2000; 20: 4941-7.
15. Tatsuta M, Yamamura H, Yamamoto R, et al. Carcinoembryonic antigen in the bile in patients with pancreatic and biliary cancer. Cancer 1982; 50: 2903-9.
16. Ker CG, Chen JS, Lee KT, et al. Assessment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. J Gastroenterol Hepatol 1991; 6: 505-8.
17. Buffet C, Fourre C, Altman C, et al. Bile levels of carcinoembryonic antigen in patients with hepatopancreatobiliary disease. Eur J Gastroenterol Hepatol 1996; 8: 131-4.
18. Paganuzzi M, Onetto M, de Paoli M, et al. Carcinoembryonic antigen (CEA) in serum and bile of colorectal cancer patients with or without detectable liver metastases. Anticancer Res 1994; 14: 1409-12.
19. Ohshio G, Manabe T, Watanabe Y, et al. Comparative studies of DU-PAN-2, carcinoembryonic antigen, and CA19-9 in the serum and bile of patients with pancreatic and biliary tract diseases: evaluation of the influence of obstructive jaundice. Am J Gastroenterol 1990; 85: 1370-6.