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Original Article

Elevated serum level of carbohydrate antigen 19-9 in benign biliary stricture diseases can reduce its value as a tumor marker

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Abstract: Although carbohydrate antigen (CA19-9) level is frequently upregulated in pancreatobiliary cancer, it is also elevated in some benign diseases. This study aimed to determine whether CA19-9 levels could be used to distinguish between benign obstructive jaundice and pancreatobiliary cancer. Fifty-seven patients with obstructive jaundice were studied retrospectively. Endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy, stone extraction, or stent placement were used to treat patients with benign bile duct stricture or inoperable malignant biliopancreatic diseases, whilst surgery was performed in suitable cases. Serum CA19-9 levels and some additional biochemical parameters were evaluated before and after treatment. CA19-9 levels were elevated in most patients, along with levels of total bilirubin, alkaline phosphatase (ALP), and gamma glutamyl transpeptidase (GGT), and 10 patients with benign disorders had extraordinarily high levels of these markers (> 1000 U/mL). The mean CA19-9 level in the malignant group was greater than that in the benign group (826.83 ± 557.34 vs. 401.92 ± 483.92 U/mL, $P = 0.005$), and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CA19-9 were 100%, 7.69%, 33.33% and 47.47%, respectively. CA19-9 levels in the whole cohort were correlated with ALP ($r = 0.77$, $P < 0.001$), GGT ($r = 0.83$, $P < 0.001$), bilirubin ($r = 0.69$, $P < 0.001$), and CRP ($r = 0.37$, $P = 0.004$). The reduction in serum level of CA19-9 after treatment in the malignant group was remarkably less than that observed in the benign group (97.26 ± 123.24 U/mL vs. 352.71 ± 397.29 U/mL, $P < 0.001$). CA19-9 levels may not be sufficient to distinguish between malignant and benign obstructive jaundice diseases.

Keywords: Carbohydrate antigen 19-9, biliary stricture disease, pancreatobiliary neoplasm, tumor maker

Introduction

Bile tract strictures have several different pathologies, including malignant and benign conditions. The latter, including inflammatory stricture secondary to choledocholithiasis, Mirizzi syndrome, extrahepatic localized form of primary sclerosing cholangitis (PSC), idiopathic benign focal stricture, and benign tumors, are possible differential diagnoses of bile duct carcinoma [1, 2]. Current imaging modalities can reliably distinguish many of these entities. However, cases in which obstructive jaundice and dilated ducts present together can lead to a misdiagnosis because of the high degree of similarity between benign and malignant biliary diseases in terms of clinical manifestations and imaging findings using ultrasound (US), magnetic resonance cholangiopancreatography (MRCP), and/or computerized tomography (CT). It is therefore desirable to have a serological test that can rapidly differentiate between benign and malignant conditions of this tissue in order to allow the prioritization of patients with malignancy and to avoid possible surgical complications in benign cases where surgery is unnecessary. However, to the best of our knowledge, no such test is currently available.

Carbohydrate antigen 19-9 (CA19-9), first isolated by Koprowski in 1979 [3], was initially considered to be a tumor marker associated with colon cancer, but was later found to be a useful tumor marker for pancreatobiliary malignancies [4, 5]. Steinberg [6] reported that a CA19-9

value > 1,000 U/mL usually indicated digestive tract cancer and had a specificity > 99% for pancreatic cancer. This finding suggests that CA19-9 is a suitable marker for distinguishing malignant pancreatobiliary disease from jaundice or a dilated bile duct. However, CA19-9 is also upregulated in other malignant tumors, including gastric, ovarian, hepatocellular, and colorectal carcinoma, as well as many benign conditions of the biliary tree, suggesting that CA19-9 may not be suitable for distinguishing between benign or malignant disease [7-10]. In a situation similar to that encountered with carcinoembryonic antigen (CEA) in colorectal cancer and CA125 in ovarian cancer, where clinical findings were contradictory, the American Society of Clinical Oncology (ASCO) does not currently advocate the use of CA19-9 for screening, evaluation of resectability, or disease follow-up in cases of pancreatobiliary tumors. Therefore, it remains unclear whether CA19-9 should be used in the clinical investigation of patients with biliary tract diseases.

In this study, we found that the specificity, positive predictive value (PPV), and negative predictive value (NPV) for CA19-9 in distinguishing between benign and malignant disease were relatively low, despite levels being higher in the malignant group. Our findings suggest that the serum level of CA19-9 cannot be regarded as a gold standard for diagnosis, but rather as a helpful adjunct when attempting to identify biliary malignancy.

Materials and methods

Study subjects

Between May 2005 and May 2008, 57 consecutive patients admitted to our department with a diagnosis of obstructive jaundice were studied retrospectively. The preliminary diagnosis was based on findings of a liver function test, ultrasonography, MRCP, and/or CT. All the detailed clinicopathological and follow-up outcome data were collected from hospital notes, physician records, or the patients themselves. This study was approved by the ethical committee of Taizhou People's Hospital, Jiangsu Province, P. R. China, and strictly adhered to the Helsinki Declaration. In 15 cases that were initially unidentified, the actual etiology was correctly identified through pathological examination or comprehensive imaging modalities after treatment. All subjects provided written informed consent.

Methods

Levels of CA19-9, ALP, GGT, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, and C reaction protein (CRP) were determined at the time of admission for all patients. The patients included in our study underwent ultrasonography (US), helical CT, and MRCP before treatment. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) was used in benign or inoperable malignant cases, and surgery was used in some appropriate cases of pancreatobiliary cancer and for some patients with benign disease who were initially diagnosed with a malignant disorder. For malignant disease, a histological diagnosis was required for categorization purposes, but for benign disease, a conclusive radiological diagnosis and 3-year clinical follow-up data were deemed adequate. Serum levels of CA19-9, ALP, GGT, AST, ALT, CRP, and bilirubin were measured again 14 days after treatment. The upper normal limit of CA19-9 serum concentration was 37 U/mL.

Statistics

Statistical analysis was performed using the SPSS 19 package program. One-way ANOVA and the paired Student's t test were used to compare continuous variables. The Pearson correlation test was used to assess the correlation of CA19-9 levels to those of other biochemical markers. For all tests, a p value < 0.05 was considered significant.

Results

Demographic characteristics of subjects

Fifty-seven patients with bile tract stricture and obstructive jaundice were studied. The age of these patients ranged from 32 to 82 years (mean ± standard deviation, 59.56 ± 13.22 years). The majority of patients (35) were female. The etiology of malignant disease was cholangiocarcinoma in 10 cases, papillary carcinoma in 2 cases, and pancreatic head carcinoma in 6 cases, whilst common bile duct (CBD) stone and inflammatory stricture were the most frequent pathology in the benign group, being present in 39 cases.

Table 1. Demographic characteristics and clinical laboratory parameters in the patients studied

Variables		Values
Total number of patients (n)		57
Age (years)		59.56 ± 13.22
Gender	Female	35
	Male	22
Etiology	Malignant	18
	Benign	39
CA19-9 (mean ± SD, U/ml)		536.11 ± 541.22
ALP (mean ± SD, U/L)		420.37 ± 358.17
GGT (mean ± SD, U/L)		416.77 ± 344.82
ALT (mean ± SD, U/L)		109.65 ± 64.99
AST (mean ± SD, U/L)		99.23 ± 57.07
T-bil (mean ± SD, μmol/L)		119.19 ± 53.48
CRP (mean ± SD, mg/L)		41.09 ± 14.69

Table 2. Comparison of clinical parameter between variable groups

Parameters (mean ± SD)	Values in variety of groups		*P* value
	Benign (n = 39)	Malignant (n = 18)	
CA19-9 (U/ml)	401.92 ± 483.92	826.83 ± 557.38	0.005
ALP (U/L)	296.87 ± 327.90	687.94 ± 267.30	0.000
GGT (U/L)	297.15 ± 326.01	675.94 ± 223.93	0.000
ALT (U/L)	110.67 ± 62.26	89.78 ± 27.71	0.018
AST (U/L)	104.18 ± 53.24	81.61 ± 17.41	0.086
T-bil (μmol/L)	94.74 ± 35.21	172.17 ± 48.02	0.000
CRP (mg/L)	48.38 ± 16.56	36.11 ± 7.71	0.082

Pre-treatment levels of CA19-9 and other biochemical markers

The demographic characteristics and laboratory biochemical parameters of these patients are listed in **Table 1**. The normal range of CA19-9, ALP, GGT, ALT, AST, total bilirubin, and CRP levels used in our hospital were 0 to 37 U/mL, 39 to 117 U/L, 11 to 49 U/L, 11 to 40 U/L, 15 to 40 U/L, 25 to 125 μmol/L, and 0 to 10 mg/L, respectively. Almost every patient in our study had an elevated serum CA19-9 level, and 10 patients with benign disease had an extremely high concentration (> 1000 U/mL). The serum level of total bilirubin (TBIL), ALP, and GGT was high in all patients, and the serum level of ALT and AST was predominantly high in benign cases. The mean serum CA19-9 level in the entire study cohort was 536.11 ± 541.22 U/mL. The average serum CA19-9 concentration was significantly higher in patients with malignant disease (826.83 ± 557.34 U/mL) than in patients with benign disease (401.92 ± 483.92 U/mL) ($P = 0.005$). However, when 37 U/mL was used as a cut-off value, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CA19-9 were 100%, 7.69%, 33.33%, and 47.47%, respectively. Furthermore, significant differences in ALP, GGT, and TBIL levels were identified between the malignant and benign groups (687.94 ± 267.30 U/mL vs. 296.87 ± 327.90 U/mL, $P < 0.001$; 675.94 ± 223.93 U/mL vs. 297.15 ± 326.01 U/mL, $P < 0.001$; and 172.17 ± 48.02 U/mL vs. 94.74 ± 35.21, $P < 0.001$, respectively) (**Table 2**). In addition, for the whole cohort, there was a significant correlation between the serum CA19-9 level and levels of TBIL ($r = 0.69$, $P < 0.001$), ALP ($r = 0.77$, $P < 0.001$), GGT ($r = 0.83$, $P < 0.001$), and CRP ($r = 0.37$, $P = 0.004$). However, while there was a significant association of CA19-9 with ALP, GGT, and TBIL in the benign group, there was no significant association between CA19-9 and these markers in the malignant group.

Post-treatment levels of CA19-9 and other biochemical markers

After treatment, which consisted of either surgery or interventional therapy, the serum level of ALP, GGT, TBIL, and CRP had reduced in both groups (**Table 3**), to within the normal range in most cases. However, the serum level of CA19-9 in the malignant group reduced by a markedly lesser extent than that in the benign group (97.26 ± 123.24 U/mL vs. 352.71 ± 397.29 U/mL, $P < 0.001$). Almost every patient with malignant disease still had a high level of CA19-9 after treatment, except for those who underwent surgery.

Nineteen of these 57 patients had extraordinarily high levels of CA19-9 (> 1000 U/mL) before treatment, 10 of whom were found to have benign disease such as choledocholithiasis and inflammatory stricture, including 5 patients originally thought to have a malignant disorder and who underwent resection on this basis. All 10 patients with extremely high CA19-

Table 3. Serum level of CA19-9 and biochemical parameters before and after treatment

Values (mean ± SD)	Total member		*P* value	Benign group		*P* value	Malignant group		*P* value
	Before	After		Before	After		Before	After	
CA19-9 (U/ml)	536.11 ± 541.22	162.61 ± 246.64	0.000	401.92 ± 483.92	50.51 ± 32.91	0.000	826.83 ± 557.38	628.22 ± 387.81	0.000
ALP (U/L)	420.37 ± 358.17	92.00 ± 77.10	0.000	296.87 ± 327.90	67.15 ± 56.38	0.000	687.94 ± 267.30	145.83 ± 89.39	0.000
GGT (U/L)	416.77 ± 344.82	98.18 ± 84.59	0.000	297.15 ± 326.00	69.74 ± 56.14	0.000	675.94 ± 223.93	159.78 ± 103.20	0.000
ALT (U/L)	109.65 ± 64.99	43.28 ± 15.40	0.000	110.67 ± 62.26	37.33 ± 9.67	0.000	89.78 ± 27.71	56.17 ± 17.75	0.000
AST (U/L)	99.23 ± 57.07	42.74 ± 14.94	0.000	104.18 ± 53.24	37.15 ± 10.11	0.000	81.61 ± 17.41	54.83 ± 16.73	0.000
T-bil (μmol/L)	119.19 ± 53.48	42.53 ± 15.82	0.000	94.74 ± 35.21	35.64 ± 8.96	0.000	172.17 ± 48.02	57.44 ± 17.35	0.000
CRP (mg/L)	41.09 ± 14.69	24.51 ± 4.57	0.000	43.39 ± 16.57	23.10 ± 3.17	0.000	36.11 ± 7.71	27.56 ± 5.65	0.000

9 levels had a good outcome after treatment, although some underwent surgery unnecessarily after 3 years of follow-up.

Discussion

Biliary diseases, especially choledocholithiasis, are prevalent in our region of China, owing in part to the eating habits of the local population and the poor quality of drinking water. In certain circumstances, some bile duct stricture disorders may be mistaken as malignant disease because of similar clinical, biochemical, and imaging findings. It has recently been suggested that some markers, particularly serum CA19-9, enhance the diagnostic potential of advanced imaging modalities such as CT, MRCP, and endoscopy ultrasonography (EUS), thus aiding diagnosis in these complex cases [2, 11]. In contrast, Jalanko H et al [12] showed that CA19-9 levels are moderately elevated in 15-36% of patients with benign pancreatic, liver, and biliary tract diseases. Some other researchers have also demonstrated that CA19-9 levels are elevated in benign biliary disorders such as choledocholithiasis and Mirizzi's syndrome [13-16]. They suggested that CA19-9 is not a suitable marker for distinguishing between malignant and benign conditions. Therefore, in the present study, we measured the serum level of CA19-9 along with that of some other biochemical markers in a cohort of patients with biliary obstructive disorders in order to investigate the diagnostic potential of these markers for identifying malignant disease.

In our study, all 57 patients presented with jaundice and dilatation of the bile duct. Eighteen patients were ultimately diagnosed with malignant pancreatobiliary disease whereas the other 39 patients had benign conditions, mostly calculus in the bile duct, which is a common disease in our region. Patients with a malignant stricture were on average older than patients in the benign group, consistent with the findings of a previous study in which malignant pancreatobiliary disorders were found to be more prevalent amongst older patients [2, 17]. Interestingly, we found elevation of serum CA19-9 in most patients with obstructive jaundice and either a pancreatobiliary tumor or choledocholithiasis. In addition, 10 patients with benign stricture (10/39) had extremely high levels of serum CA19-9 (> 1000 U/mL). Overall, significantly more patients were positive for CA19-9 in the malignant group than in the benign group when using 37 U/mL as a cut-off, based on previous studies [2, 4]. However, unfortunately, despite a very high sensitivity for malignant disease, the specificity, PPV, and NPV using CA19-9 were low, which could lead to many benign biliary stricture disorders being mistaken for a malignant condition. Some studies, mostly published as case reports, showed highly elevated levels of CA19-9 in benign strictures involving cystic and common bile duct lithiasis, Mirizzi's syndrome, and several other conditions [8, 18, 19]. Furthermore, Dogan et al. recently found that CA19-9 levels were elevated in 32 patients with choledocholithiasis (46%), including 8 patients (11%) who had very high levels of CA19-9 (> 1000 U/mL). On the basis of these studies, we considered whether CA19-9 is not a suitable marker for distinguishing between benign and malignant obstructive jaundice disease. The diagnostic value of CA19-9 might be improved by using a more appropriate cutoff value, although establishing this cutoff value requires further and larger prospective studies. Nevertheless, in two other studies, CA19-9 could distinguish between benign and malignant pancreaticobiliary disease [20, 21]. However, in both these studies, the CA19-9 levels in the benign groups were relatively low, and none exceeded 243 U/mL, in contrast with the subjects included in our study. Furthermore, many of the patients in these previous studies did not have jaundice.

In clinical practice, some patients with a benign stricture can have an extremely high level of serum CA19-9. Cholangitis may result in high serum levels of CA19-9 [22]. Kim et al [23] also considered that CA19-9 was a more useful diagnostic marker for patients without cholangitis or cholestasis. The presence of cholangitis and a long history of benign stricture might contribute to the decrease in specificity of CA19-9 among patients with obstructive jaundice. In our region, many patients were not diagnosed early, and treatment was therefore delayed because of a lack of experience on the part of the primary care doctors. As a result, most patients in our study had a relatively long history and usually presented with cholangitis confirmed through increase in CRP level. Thus, the different clinical background of the patients in these studies may have contributed to their conflicting results.

CA19-9 is a serum glycoprotein and can be secreted by epithelial cells in the pancreas, biliary tract, and other digestive ducts; therefore, it is not surprising that CA19-9 level is elevated in gastrointestinal carcinomas. However, it is less clear why CA19-9 level is elevated in some benign diseases, especially biliary obstructive disorders. von Ritter et al [24] found that mucins secreted from normal human gallbladder epithelial cells (HGBECs) carried the CA19-9 epitope and that during inflammatory biliary disease, leakage of biliary mucins into serum may led to the non-specific elevation of CA19-9 in serum. Another possible source might be irritated bile duct cells exposed to increased biliary pressure and the increased proliferation of epithelial cells due to inflammation [23, 25]. Therefore, as every subject in our study presented with typical obstructive jaundice, malignant or benign, almost all of these patients had elevated serum levels of CA19-9. This might explain the different results regarding the diagnostic potential of CA19-9, whereby it could distinguish between benign and malignant biliary disease in studies with cohorts in which almost 50% of the patients did not have jaundice.

In addition to an elevated level of serum CA19-9, other biochemical markers were also found to be present at abnormal levels in our study. ALP, GGT, ALT, AST, total bilirubin, and CRP were elevated in most patients. After treatment using interventional therapy or surgery, CA19-9 levels declined in many cases along with levels of other markers such as TBIL, ALP, and GGT, particularly in patients with benign disease. Thus, the CA19-9 level was positively associated with the level of TBIL, ALP, and GGT, especially in the benign group, which concurs with the findings of previous studies [2]. However, the reduction in serum CA19-9 in the malignant group was significantly less than that in the benign group, except in some cases in which the obstructing mass had been removed. The serum level of CA19-9 in many patients with pancreaticobiliary cancer did not decrease back to within the normal range, which is partly attributable to the uncontrolled growth of aberrant epithelial cells and their continuous secretion of this antigen. In contrast, most cases of benign disease showed a full clinical and biochemical recovery. Thus, elevated CA19-9 level should be interpreted cautiously in patients with obstructive jaundice, unless these high levels persist after the obstruction has been removed. A repeat assay for CA19-9, performed 2 or 3 weeks after resolution of jaundice, may help in differentiating between malignant and benign strictures.

In conclusion, although only a few patients were included in this study, the results suggest that CA19-9 levels alone cannot differentiate between malignant and benign obstructive jaundice upon initial presentation. However, assessing serum CA19-9 at specific, clinically relevant time points, for example after the obstruction has been cleared, together with clinic features and imaging results, might have significant potential diagnostic utility. A larger, prospective study may be needed to confirm our results.

Disclosure of conflict of interest

None.

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