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ORIGINAL ARTICLE

Etiologies of remarkably elevated serum levels of carbohydrate antigen 19-9

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Summary

Purpose: *To investigate the etiologies of remarkably elevated serum levels of CA 19-9.*

Methods: *During January 2014 to June 2020 patients with CA 19-9>1000 U/ml were included. The frequencies of distant metastases for malignant patients and serum levels of carbohydrate embryonic antigen (CEA) and carbohydrate antigen 125 (CA 125) were analyzed.*

Results: *Of the 125 patients included, 113 (90.4%) were diagnosed with malignancy, 100 (80%) with digestive cancer and only 36 (28.8%) with pancreatic cancer (PC). In patients with malignancy, 75 (66.3%) had distant metastasis and 60 (53.1%) had liver metastasis. The median levels of CEA and CA 125 in patients with malignant disease were significantly higher than in patients with benign disease (19.05 ng/ml versus 3.16 ng/ml, p=0.01; 83.32 U/ml versus 18.35 U/ml, p=0.01, respectively).*

Conclusions: *CA 19-9>1000U/ml indicated a high probability of having malignant disease, especially digestive cancer, but not always PC. Patients with malignant disease had high proportion of distant metastasis, mostly in the liver. Combined tests of CEA and CA 125 had potential role in distinguishing between benign and malignant diseases.*

Key words: *CA 19-9, etiology, digestive cancer, CEA, CA 125*

Introduction

Carbohydrate antigen 19-9 (CA 19-9) was originally discovered by Koprowski et al in 1979 [1] and thereafter was widely used as a tumor marker in the diagnosis of pancreatic cancer (PC). A recently published meta-analysis found that serum levels of CA 19-9 over 37 U/ml had both sensitivity and specificity of 80% to detect PC [2]. However, the clinical utility of CA 19-9 as a diagnostic test for PC is increasingly under debate in recent years. CA 19-9 is not reliable for cancer screening in healthy individuals due to a low positive predictive value (PPV) [3-5]. In addition, CA 19-9 is not specific to PC, but is well associated with many extra-pancreatic malignant diseases, especially digestive cancers. Previous studies reported that the specificity of CA 19-9 for PC increased with increasing serum levels, eventually, reaching nearly 100% specificity for levels above 1000 U/ml [6]. However, several case reports recently showed that some benign diseases could also result in remarkably elevated serum levels of CA 19-9 [7-10]. To overcome the diagnostic limitations of a single test, multiple tumor markers such as carbohydrate embryonic antigen (CEA) and carbohydrate antigen 125 (CA 125) are often used in conjunction with CA 19-9. Several studies have shown that the use of multiple tumor markers can improve the diagnostic performance of CA 19-9 in malignant diseases and hence they are widely used in clinical practice [11-13].

Furthermore, remarkably elevated serum levels of CA 19-9 associated with malignancies often do not occur until the disease advances. Increased level

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of CA 19-9 has a potential role in predicting disease prognosis and response to treatment for patients with malignancies. Yet, to the best of our knowledge, the disease spectrum in patients with remarkably elevated serum levels of CA 19-9 has not been reported. Therefore, the purpose of our study was to investigate the etiologies of remarkably elevated serum levels of CA 19-9 and evaluate the clinical features for those patients with malignant diseases.

Methods

Subject selection and classification

Patients who had undergone blood tests for CA 19-9 at Beijing Tian Tan Hospital from January 2014 to June 2020 were retrieved from the electronic medical record system. All patients with serum levels of CA 19-9 above 1000 U/ml were included in the study if their etiology behind the elevated levels was retrievable. Patients with an undetermined diagnosis or incomplete information were excluded from the study. For patients with multiple eligible tests of CA 19-9, only results with the highest values were recorded. To facilitate data analysis, the patients were divided into benign and malignant groups. The malignant group was further subdivided into patients with digestive and non-digestive cancers. The patients in the digestive cancer group were subsequently classified into hepatobiliopancreatic cancer group which included patients diagnosed with PC, cholangiocarcinoma, or gallbladder cancer, and gastrointestinal cancer group which included patients diagnosed with colorectal, gastric, and small intestine cancers.

Determination of etiologies

The etiologies of remarkably elevated serum levels of CA 19-9 were determined using the following criteria:

1. Hepatobiliopancreatic cancers were diagnosed by histological examinations or typical findings of radiological examinations including contrast-enhanced computed tomography (CECT) and/or positron emission tomography-computed tomography (PET-CT).
2. Gastrointestinal cancers were all diagnosed by histological examinations.
3. Other non-digestive cancers were diagnosed by histological examinations or typical findings of radiological examinations including CECT and/or PET-CT.
4. Acute pancreatitis (AP) was diagnosed by the concurrence of at least two of the following findings: 1) typical abdominal pain, 2) serum amylase activity at least three times greater than the upper limit of normal (ULN), and 3) characteristic findings on CT or transabdominal ultrasound (TUS) [14].
5. Common bile duct stone was diagnosed by typical findings of filling-defect in common bile duct by magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic retrograde cholangiopancreatography (ERCP).

Before benign diseases were diagnosed, patients should be followed up for at least 6 months to exclude malignant disease.

Variables and measurements

Levels of serum tumor markers, including CA 19-9, CEA, and CA 125 were detected by the electrochemical luminescence method. The upper limit of normal (ULN) for serum CA 19-9, CEA, and CA 125 levels were 37 U/ml, 5 ng/ml, and 35 U/ml, respectively. All radiological examinations were read and reported by two experienced radiologists and all histological evaluations were performed by two experienced pathologists. The etiologies of the patient with CA 19-9 above 1000 U/ml, demographic data (age and gender), and levels of serum CA 19-9, CEA and CA 125 were recorded in a predesigned data collection table. The percent number of patients with malignant diseases presenting with distant metastasis in the liver, lung, and other site metastases were also recorded.

Statistics

Categorical variables were described as percents and compared by the Pearson x^2 test or Fisher's exact test, depending on the expected frequencies. Continuous variables with normal distribution were described as mean ± standard deviation and compared by independent-samples *t*-test. Continuous variables with skewed distribution were presented as median values and interquartile ranges (IQR) and analyzed by using the Mann-Whitney U test. P value less than 0.05 was considered statistically significant. P values were two-sided. All statistical analyses were performed with SPSS for Windows, version 22.0 (Chicago, IL, United States).

Results

Study inclusion

A total of 54,008 tests of CA 19-9 were extracted from the electronic medical record database. Among them, 226 tests showed CA 19-9 levels

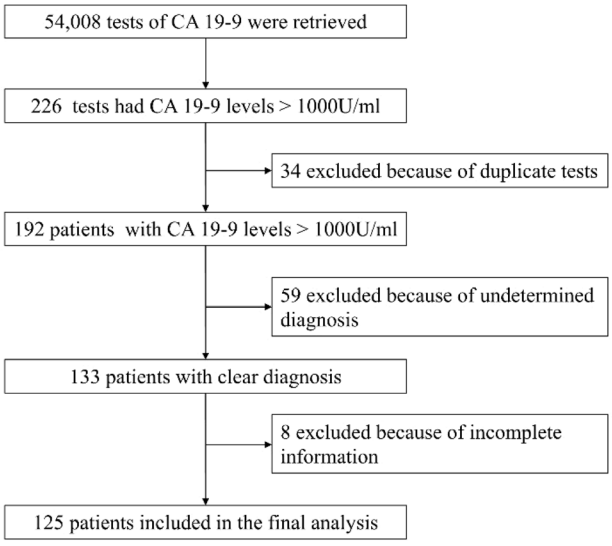

Figure 1. Study flowchart. CA 19-9: carbohydrate antigen 19-9.

above 1000 U/ml, accounting for 0.42% of the total tests. One hundred and ninety-two patients with CA 19-9 levels above 1000 U/ml were identified after excluding 34 duplicate tests on the same patients. Fifty-nine patients with undetermined diagnosis and 8 patients with incomplete information were further excluded, leaving 125 patients for analysis (Figure 1). The mean age was 63.83±12.27 years and the median serum level of CA 19-9 was 2666.0 (1543.5-6201.5) U/ml.

Causes of remarkably elevated serum levels of CA 19-9

Of the total, most of the patients (113, 90.4%) were diagnosed with malignant disease. One hundred patients were diagnosed with digestive cancer, accounting for 80% of all patients with CA 19-9 levels above 1000 U/ml; the other 13 (10.4%) patients were diagnosed with non-digestive cancer. Sixty-one (48.8%) patients were diagnosed with hepatobiliopancreatic cancer while the other 39 (31.2%) patients were diagnosed with gastrointestinal cancer (Table 1).

Only 36 (28.8%) of patients with CA 19-9 levels above 1000 U/ml were diagnosed with PC. The other malignant etiologies, were colorectal cancer (n=22, 17.6%), cholangiocarcinoma (n=20, 16%), gastric cancer (n=14, 11.2%), lung cancer (n=11, 8.8%), gallbladder cancer (n=5, 4.0%), small intestine cancer (n=3, 2.4%), and urogenital cancer (n=2, 1.6%). The remaining 12 (9.6%) patients were diagnosed with benign disease, including 9 (7.2%) patients with common bile duct stone and 3 (2.4%) patients with AP (Figure 2). The males accounted for 54.9% of malignant patients and 83.3% of benign patients. The mean age was 63.56±12.00 years for malignant patients and 66.42±14.93 years for benign patients. Gender (p=0.06) and age (p=0.45) had no significant impact on the prevalence of benign and malignant disease.

Distant metastases in patients with malignant disease

Seventy-five (66.3%) patients were diagnosed with distant metastases with the liver being the most common site of metastasis (53.1%), followed

Table 1. Demographic data of patients with CA 19-9 serum levels above 1000 U/ml

Etiology	*Cases* *n (%)*	*Male* *n (%)*	*Age* *Mean ± SD*
Malignant disease	113 (90.4)	62 (54.9)	63.56±12.00
Digestive cancer	100 (80.0)	55 (55.0)	63.38±12.16
Hepatobiliopancreatic cancer	61 (48.8)	33 (54.1)	65.33±10.40
Gastrointestinal cancer	39 (31.2)	22 (56.4)	60.33±14.11
Non-digestive cancers	13 (10.4)	7 (53.8)	64.92±11.03
Benign disease	12 (9.6)	10 (83.3)	66.42±14.93

SD: standard deviation.

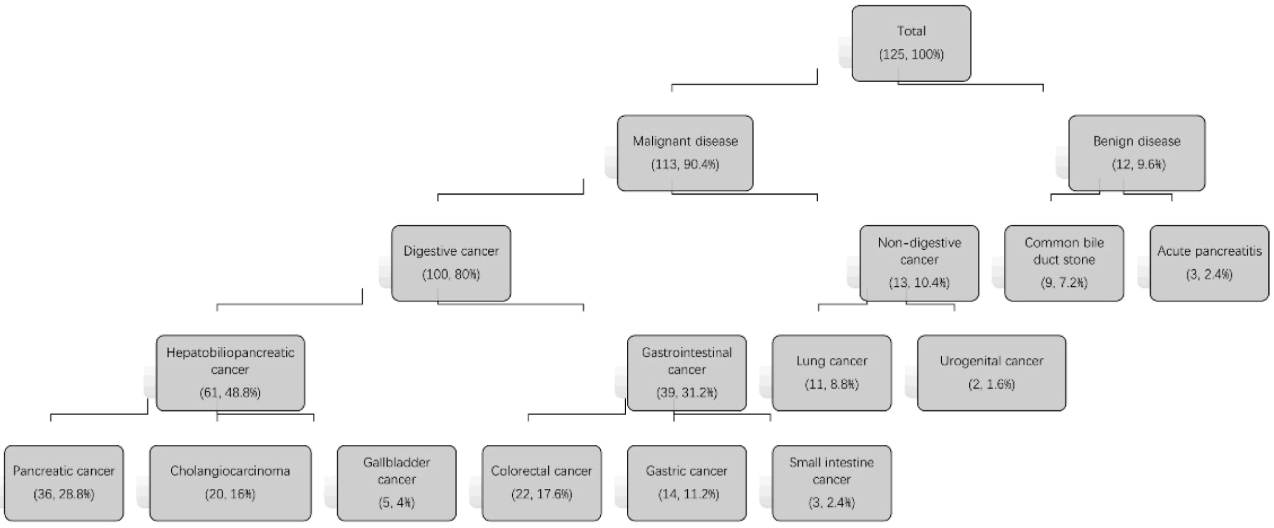

Figure 2. Etiologies of remarkably elevated serum levels of CA 19-9.

by the lung (13.3%) and other sites (18.6%). The percentage of liver metastases in the digestive cancer group was significantly higher than in the non-digestive cancer group (57.0% versus 23.1%; p=0.02), while the percentage of other site metastases in the digestive cancer group was significantly lower than in the non-digestive cancer group (13.0% versus 61.5%; p<0.01). There was no statistically significant difference between the digestive cancer group and the non-digestive cancer group considering the percentage of total metastases (p=0.21) and lung metastasis (p=0.07) (Table 2). In patients with digestive cancer, the percentages of total distant metastases and liver metastasis in the gastrointestinal cancer group were significantly higher than in the hepatobiliopancreatic cancer group (84.6% versus 50.8%; p<0.01 and 71.8% versus 47.5%; p=0.02, respectively). There was no statistically significant difference between the gastrointestinal cancer group and hepatobiliopancreatic cancer group in the percentage number of metastasis occurring in the lung (p=0.33) and other sites (p=0.24). (Table 3).

Relationship between other commonly used serum tumor markers and etiologies of elevated CA 19-9

The median serum levels of both CEA (3.16 ng/ml) and CA 125 (18.35 U/ml) were in the normal range in patients with benign disease. The median value of serum CEA level in patients with malignant disease was increased to 19.05 ng/ml, which was significantly higher than that in patients with benign disease (p=0.01). The median value of serum CA 125 level in patients with malignant disease was increased to 83.32 U/ml, which was also significantly higher than that in patients with benign disease (p=0.01). In patients with malignant disease, the median level of CA 125 in the non-digestive cancer group was significantly higher

Table 2. Comparison of distant metastases in patients with digestive and non-digestive cancer

Metastases	*Total (n=113)* n (%)	*Digestive cancer (n=100)* n (%)	*Non-digestive cancer (n=13)* n (%)	*p*
Total distant metastases	75 (66.3)	64 (64.0)	11 (84.6)	0.21
Liver metastases	60 (53.1)	57 (57.0)	3 (23.1)	0.02
Lung metastases	15 (13.3)	11 (11.0)	4 (30.8)	0.07
Other sites metastases	21 (18.6)	13 (13.0)	8 (61.5)	<0.01

Table 3. Comparison of distant metastases between patients with gastrointestinal cancer and hepatobiliopancreatic cancer

Metastases	*Total (n=100)* n (%)	*Gastrointestinal cancer (n=39)* n (%)	*Hepatobiliopancreatic cancer (n=61)* n (%)	*p*
Total distant metastases	64 (64.0)	33 (84.6)	31 (50.8)	<0.01
Liver metastases	57 (57.0)	28 (71.8)	29 (47.5)	0.02
Lung metastases	11 (11.0)	6 (15.4)	5 (8.2)	0.33
Other site metastases	13 (13.0)	7 (17.9)	6 (9.8)	0.24

Table 4. Comparison of CEA and CA 125 between different disease groups in patients with CA 19-9 above 1000 U/ml

Etiology	*CEA, ng/ml*		*CA125, U/ml*	
	Median (IQR)	*p*	*Median (IQR)*	*p*
Total				
Malignant disease	19.05 (6.14-268.45)		83.32 (24.68-266.90)	
Benign disease	3.16 (2.38-4.66)	0.01	18.35 (10.81-27.54)	0.01
Malignant disease				
Digestive cancer	17.30 (6.11-213.40)		70.07 (21.02-222.50)	
Non-digestive cancer	33.73 (14.36-716.95)	0.34	242.95 (79.16-875.35)	0.04
Digestive cancer				
Hepatobiliopancreatic cancer	10.15 (5.43-51.73)		57.22 (17.21-205.67)	
Gastrointestinal cancer	146.32 (9.01-1415.68)	<0.01	81.66 (29.32-263.83)	0.49

than the digestive cancer group (242.95 U/ml versus 70.07 U/ml; p=0.04). There was no statistically significant difference between the digestive cancer group and the non-digestive cancer group considering the median level of CEA (p=0.34). In patients with digestive cancer, the median level of CEA in the gastrointestinal cancer group was 146.32 ng/ml, which was significantly higher than that of 10.15 ng/ml in the hepatobiliopancreatic cancer group (p<0.01). There was no statistically significant difference between the gastrointestinal cancer group and hepatobiliopancreatic cancer group in the median level of CA 125 (p=0.49) (Table 4).

Discussion

Our present study found that the etiologies leading to remarkably elevated CA 19-9 levels varied widely. Most of patients with malignant origins had cancer in the digestive system. Although PC was the most common single disease in patients with CA 19-9 above 1000 U/ml, this accounted for only 28.8% of all cases. Although benign biliary-pancreatic disease was the least common etiology leading to remarkably elevated CA 19-9, it still accounted for nearly 10% of all cases.

Elevated CA 19-9 is a promising predictor of poor prognosis for patients with certain digestive cancers. Wang et al has reported that serum CA 19-9 level is the most significant prognostic indicator for patients with metastatic colorectal cancer [15]. Serum CA 19-9 has been used for the assessment of preoperative staging and resectability for PC [16,17]. Distant metastasis is often the final stage of malignant diseases and has a very poor prognosis. The present study showed that nearly two-thirds of the patients with malignant disease had distant metastases with liver metastasis occurring in more than 50% of these patients. Patients with digestive cancer, especially gastrointestinal cancer, had a high percentage of liver metastasis. Our findings were consistent with previous reports and provided more information about distant metastasis.

Other serum tumor markers, such as CEA and CA 125, are often ordered together with CA 19-9 in clinical practice to improve the diagnostic performance. In our study, we found that there were significant differences between the malignant group and benign group considering CEA and CA 125 levels, between the digestive cancer group and non-digestive cancer group considering CA 125 level, and between the gastrointestinal cancer group and hepatobiliopancreatic cancer group considering CEA level. The above findings indicated that CEA and CA 125 might be useful for differential diagnosis in patients with CA 19-9 levels above 1000 U/ml.

The mechanism leading to elevated serum CA 19-9 remains unclear, which is probably due to the imbalance in the production and metabolism of this biomarker. CA 19-9 is a high-molecular-weight mucinous glycoprotein and widely expressed by epithelial cells, including pancreatic and biliary ductal epithelial cells [1,18,19]. In epithelial cancers, the expression of CA 19-9 is up-regulated by rapidly multiplying cells, resulting in elevated serum CA 19-9 level, which increases to high levels as the disease progresses. Serum CA 19-9 levels can be elevated in some benign diseases, especially biliary-pancreatic diseases. In most instances, the elevation of CA 19-9 in benign diseases is mild to moderate. A previous study reported that only 4.7% of patients with acute cholangitis or cholestasis had a remarkable serum level of above 1000 U/ml [20]. Nevertheless, our study showed that nearly 10% of patients with CA 19-9 above 1000 U/ml were diagnosed with common bile duct stones or acute pancreatitis. The mechanism of elevated CA 19-9 in benign biliary-pancreatic diseases is still under investigation. Inflammation and obstruction may partly explain the increase in serum level of CA 19-9. Inflammation and resultant high lumen pressure accelerate the production of CA 19-9 by increasing the proliferation of pancreatic or biliary ductal epithelial cells. Duct obstruction causes CA 19-9 to accumulate in the lumen and ultimately escapes into the circulatory system [8].

Our study has a number of limitations that have to be acknowledged. Due to the retrospective nature of this study, it was not possible to obtain all necessary information for every patient with CA 19-9 above 1000 U/ml. As a result, 67 patients with an undetermined diagnosis or incomplete information had to be excluded from the study, potentially influencing the actual proportion of the etiologies. Furthermore, the data for this study were collected from one single center, limiting the generalizability of the research findings. Finally, the etiology behind the remarkably elevated CA 19-9 serum level was mostly based on radiological examinations rather than histological examinations, which is less accurate potentially influencing the reliability of the etiology evaluations.

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Conflict of interests

The authors declare no conflict of interests.

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