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Increased CA 19-9 level in patients without malignant disease

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Abstract

Background: The measurement of carbohydrate antigen 19-9 (CA 19-9) is recommended for the diagnosis and follow-up of pancreatic cancer. However, increased CA 19-9 has also been reported in patients with various benign diseases of the lung. We aimed to elucidate the pulmonary radiographic abnormalities and laboratory results associated with increased concentrations of CA 19-9.

Methods: This study was performed using a case-controlled design. Cases included all participants in a cancer screening program who had an increased CA 19-9 concentration (>37 U/mL), but without a diagnosis of malignancy. Age- and sex-matched participants with normal CA 19-9 levels were enrolled as controls. Laboratory results and radiographic features were compared.

Results: In total, 119 participants with increased CA 19-9 concentrations and 476 controls were included. A higher erythrocyte sedimentation rate (ESR) [adjusted odd ratio (aOR), 1.03; 95% confidence interval (CI), 1.01–1.05], higher hemoglobin A_{1c} (HbA_{1c}) (aOR, 1.28; 95% CI, 1.05–1.56), bronchiectasis (aOR, 2.48; 95% CI, 1.22–5.02), bronchiolitis (aOR, 3.93; 95% CI, 1.88–8.22), emphysema (aOR, 2.67; 95% CI, 1.32–5.40), and interstitial fibrosis (aOR, 10.62; 95% CI, 2.03–55.44) were independent factors for increased CA 19-9.

Conclusions: CA 19-9 concentrations, as well as increased ESR and HbA_{1c}, can be increased in patients with various lung abnormalities.

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Introduction

Carbohydrate antigen 19-9 (CA 19-9) is the sialylated Lewis (Le)[a] blood group antigen. Individuals with an Le^{a-b-} phenotype, lacking the Lewis antigen glycosyltranferase, are unable to synthesize CA 19-9 (1). Originally recognized as a tumor-associated antigen, it was defined using monoclonal antibody (1116 NS 19-9) produced from a hybridoma prepared from mouse spleen following immunization with human colorectal carcinoma cell line (2, 3). The usefulness of serum CA 19-9 concentrations for diagnosis of pancreatic cancer is well recognized (4, 5).

Increased concentrations of serum CA 19-9 have also been reported in other types of malignant, as well as in benign diseases. In particular, there are occasional reports of increased CA 19-9 in several benign lung diseases, including cystic fibrosis (6), idiopathic pulmonary fibrosis (7), pulmonary sequestration (8), and *Mycobacterium intracellular* complex lung diseases (9). However, few studies have systematically evaluated the relationship between increased CA 19-9 and non-malignant lung diseases. We attempted to elucidate the pulmonary radiographic abnormalities and laboratory results associated with an increased CA 19-9.

Materials and methods

Study design and enrollees

This study was performed using a case-controlled design. Cases and controls were selected individuals participating in a cancer screening program from 1 January 2004 to 31 December 2006 at Healthcare System Gangnam Center, a clinic for comprehensive cancer screening affiliated with Seoul National University Hospital. Participation in the cancer screening program is voluntarily and at each individuals own expense. Cases included every patient showing an increased CA 19-9 concentration (>37 U/mL), but without a diagnosis of malignancy. We included four times as many age- and sex-matched participants with normal CA 19-9 concentration as controls. The protocol for this study was approved by the Ethics Review Committee of the Seoul National University Hospital.

Protocols for the cancer screening program

Physical examinations Physical examinations, including height and weight measurements, were performed by board-certified physicians.

Laboratory tests Laboratory tests consisted of the following: leukocyte count including differential counts, hematocrit, hemoglobin, platelet count, total cholesterol, total protein, albumin, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, creatinine, electrolytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), prothrombin time, activated partial thromboplastin time, hemoglobin A_{1c} (HbA_{1c}), Venereal Disease Research Laboratory (VDRL) test, hepatitis B surface antigen, anti-hepatitis B virus antibody, anti-hepatitis C virus antibody, anti-HIV antibody, triiodothyronine, free thyroxine, thyroid stimulating hormone, urinalysis, and stool occult blood.

Radiological examinations Low-dose computerized tomography of the chest (LDCT), mammography with and without breast sonography in women, abdominal sonography or abdominal CT, and thyroid sonography were performed.

LDCT of the chest was performed using a 16-detector scanner (SOMATOM Sensation 16, Siemens Medical Systems, Munich, Germany) with the following settings: 0.75 mm collimation$\times$16 channels; 5-mm thickness reconstruction with 5-mm intervals; pitch (ratio of travel per rotation to total beam width), 1.0; 120 kVp; and 40 (120 mA/0.33 s) mAs. Lesion characterization, if necessary, was accomplished by obtaining 1 mm thin-section CT reconstruction images.

Other evaluations Pulmonary function tests, including forced expiratory volume at 1 s (FEV_1) and forced vital capacity (FVC), esophago-gastroduodenoscopy, and colonoscopy were performed.

Measurement of tumor markers Serum CA 19-9 concentrations were measured with an enzyme immunoradiometric assay kit (TFB, Tokyo, Japan). CA 19-9 concentrations >37 U/mL were considered increased (10). Serum carcinoembryonic antigen (CEA; RADIM, Rome, Italy), α-fetoprotein (AFP; Immunotech a.s., Prague, Czech Republic), carbohydrate antigen 125 (CA 125; TFB, Tokyo, Japan), and prostate-specific antigen (PSA; Cis Bio International, Gif-sur-Yvette, France) were also measured using enzyme immunoradiometric assays. Measurements were performed by technicians blinded to the clinical information about the samples.

Definition of pulmonary radiographic abnormalities

Pulmonary lesions on LDCT were evaluated by a board-certified chest radiologist blinded to the CA 19-9 level.

- Emphysema was defined by the presence of focal areas or regions of low attenuation without visible walls (11).
- Interstitial fibrosis was diagnosed if LDCT showed bilateral basilar subpleural reticulation, usually accompanied by traction bronchiectasis and architectural distortion and honeycomb cysts (12).
- Bronchiectasis was diagnosed based on findings that included dilatation of an airway lumen, rendering it more than 1.5 times the width of a nearby vessel; lack of tapering of an airway toward the periphery; varicose constrictions along airways; and ballooned cysts at the end of a bronchus (13).
- Bronchiolitis was diagnosed when lesions such as the tree-in-bud pattern, centrilobular nodules, and bronchiolar wall thickening were observed (11).
- Sequelae of pulmonary tuberculosis (TB) were identified by LDCT observations of fibrotic bands, small calcified nodules, or bronchiectasis in the upper lobes (14).

Statistical analysis

The χ^2-test for comparison of categorical variables and the t-test for comparison of continuous variables between cases and controls were applied. The variables analyzed included body mass index, comorbidities, smoking status, leukocyte count, segmented neutrophil count, eosinophil count, hematocrit, ESR, CRP, total bilirubin, AST, ALT, HbA_{1c}, creatinine, CEA, AFP, CA 125, PSA, FEV_1, FVC, and various radiographic lung abnormalities. To identify predictors for increased CA 19-9, multiple logistic regression models were constructed by including any variables with a $p<0.10$. Backward elimination was used to select the variables to be maintained in the final model. CEA, AFP, CA 125, and PSA were excluded from the final model since they could not explain the increase of CA 19-9. A Hosmer-Lemeshow Goodness of Fit (GOF) test was performed to confirm the fitness of the final model. Statistical significance was considered if $p<0.05$. All statistical analyses were performed using SPSS® (Version 12.0, Chicago, IL, USA).

Results

Baseline characteristics of enrolled patients

We evaluated 11,096 participants; 130 of which had a CA 19-9 concentration >37 U/mL (Figure 1). Of these 130 patients, 11 were excluded due to malignancy: five patients with pancreatic cancer; two with hepatocellular carcinoma; one with lung cancer; one with colon cancer; one with papillary thyroid carcinoma; and one patient with malignant teratoma. Four times as many age- and sex-matched participants with normal CA 19-9 concentrations were included as controls. Thus, a total of 119 participants with increased CA 19-9 and 476 participants with normal CA 19-9 concentrations were included in the analysis. Body mass index, smoking status, and comorbidities were not different between the two groups. However, diabetes mellitus was more common in the group of patients who had CA 19-9 >37 U/mL (22.7% vs. 11.8%, $p=0.002$). The leukocyte count, neutrophil count, ESR, HbA_{1c}, CEA, and CA 125 were higher in participants with increased CA 19-9 compared with controls (Table 1).

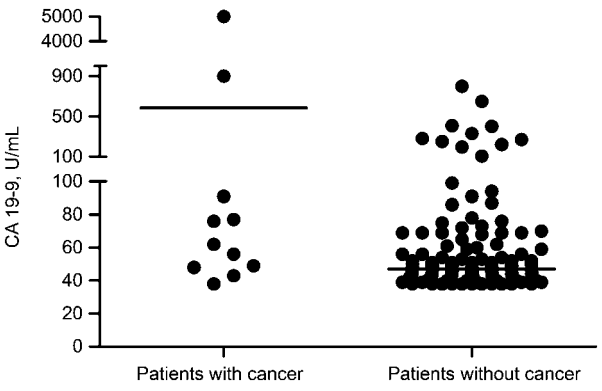

Figure 1 Serum concentrations of CA 19-9 among 130 patients with increased values (CA 19-9 >37 U/mL).

Table 1 Comparison of baseline characteristics between participants with increased and normal CA 19-9 concentrations.

	Patients with increased CA 19-9 (>37 U/mL) (n=119)	Patients with normal CA 19-9 (0–37 U/mL) (n=476)	p-Value
Age, median (range), years	56 (33–83)	56 (32–84)	0.98
Sex, female	64 (53.8%)	256 (53.8%)	1.00
Body mass index, kg/m^2	22.9±3.0	23.3±2.8	0.19
Current smoker	21 (20.6%)	77 (17.2%)	0.42
Comorbidities			
Hypertension	44 (37.3%)	143 (30.4%)	0.15
Diabetes mellitus	27 (22.7%)	56 (11.8%)	0.002
Dyslipidemia	42 (35.3%)	134 (28.2%)	0.13
Chronic liver disease	6 (5.0%)	41 (8.6%)	0.20
Laboratory findings			
White blood cell count, $\times 10^9$/L	6.26±1.98	5.63±1.66	0.002
Segmented neutrophil count, $\times 10^9$/L	3.76±1.73	3.25±1.42	0.004
Eosinophil count, $\times 10^9$/L	0.18±0.21	0.15±0.14	0.17
Hematocrit, %	42.5±4.7	42.7±4.0	0.65
Erythrocyte sedimentation rate, mm/h	13±17	8±8	0.002
C-reactive protein, g/L	0.004±0.20	0.001±0.003	0.15
Total bilirubin, μmol/L	17.45±8.27	18.76±9.48	0.17
AST, U/L	30±44	26±11	0.27
ALT, U/L	32±74	25±16	0.36
Creatinine, μmol/L	87.87±17.38	88.77±16.08	0.59
Hemoglobin A_{1c}, %	6.1±1.4	5.8±0.8	0.02
Pulmonary function tests			
Forced vital capacity, L	3.28±0.78	3.36±0.74	0.31
Forced expiratory volume in 1 s, L	2.59±0.65	2.66±0.60	0.26
FEV_1/FVC, %	79±8	80±7	0.76
Tumor markers			
CA 19-9, U/mL	78±107	10±7	<0.001
CEA, μg/L	2.3±1.6	1.6±0.9	<0.001
AFP, μg/L	7±22	5±4	0.23
PSA, μg/L	1.6±2.1	1.4±1.2	0.38
CA 125, U/mL	21±26	10±7	0.002

AST, asparatate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CA 19-9, carbohydrate antigen 19-9; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen; CA 125, carbohydrate antigen 125.

Prevalence of pulmonary radiographic abnormalities

The prevalence of pulmonary radiographic abnormalities was higher in participants with increased CA 19-9 concentrations compared to those with normal concentrations (57.1% vs. 26.9%, $p<0.001$) and sequelae of pulmonary TB was the most frequent abnormal findings (21.8% and 14.9%, respectively). All categories of pulmonary abnormalities, except sequelae of pulmonary TB, were more common in participants with increased CA 19-9 concentrations (Table 2).

Characteristics associated with increased CA 19-9

ESR, HbA_{1c}, cholecystitis, sequelae of TB, bronchiectasis, bronichiolitis, emphysema, and interstitial fibrosis were included as variables in the final multiple logistic regression model. Among these variables,

Table 2 Comparison of pulmonary parenchymal abnormalities based on low-dose chest CT between participants with increased and normal CA 19-9 concentrations.

	Patients with increased CA 19-9 (>37 U/mL) (n=119)	Patients with normal CA 19-9 (0–37 U/mL) (n=476)	p-Value
Absence of abnormal lesion	51 (42.9%)	348 (73.1%)	<0.001
Presence of abnormal lesion[a]	68 (57.1%)	128 (26.9%)	
Sequelae of pulmonary TB	26 (21.8%)	71 (14.9%)	0.07
Bronchiectasis	21 (17.6%)	26 (5.5%)	<0.001
Bronchiolitis	20 (16.8%)	22 (4.6%)	<0.001
Emphysema	18 (15.1%)	27 (5.7%)	<0.001
Interstitial fibrosis	6 (5.0%)	2 (0.4%)	0.001

[a]If two or more characteristics were present in one patient, they were counted separately. TB, tuberculosis.

Table 3 Laboratory and radiographic characteristics associated with increased CA 19-9 (multivariable analysis)[a].

	Patients with increased CA 19-9 level (>37 U/mL) (n=119)	Patients with normal CA 19-9 (0–37 U/mL) (n=476)	p-Value	OR	95% CI
ESR, mm/h[b]	13±17	8±8	0.005	1.03	1.01–1.05
HbA_{1c}, %[c]	6.1±1.4	5.8±0.8	0.02	1.28	1.05–1.56
Sequelae of pulmonary TB	26 (21.8%)	71 (14.9%)	0.13	1.55	0.88–2.71
Bronchiectasis	21 (17.6%)	26 (5.5%)	0.01	2.48	1.22–5.02
Bronchiolitis	20 (16.8%)	22 (4.6%)	<0.001	3.93	1.88–8.22
Emphysema	18 (15.1%)	27 (5.7%)	0.006	2.67	1.32–5.40
Interstitial fibrosis	6 (5.0%)	2 (0.4%)	0.005	10.62	2.03–55.44

[a]Hosmer-Lemeshow Goodness of Fit: p-value 0.700; [b](x+1 mm/h vs. x mm/h); [c](x+1% vs. x%); ESR, erythrocyte sedimentation rate; HbA_{1c}, hemoglobin A_{1c}; TB, tuberculosis.

ESR [adjusted odd ratio (aOR), 1.03; 95% confidence interval (CI), 1.01–1.05], HbA_{1c} (aOR, 1.28; 95% CI, 1.05–1.56), bronchiectasis (aOR, 2.48; 95% CI, 1.22–5.02), bronchiolitis (aOR, 3.93; 95% CI, 1.88–8.22), emphysema (aOR, 2.67; 95% CI, 1.32–5.40), and interstitial fibrosis (aOR, 10.62; 95% CI, 2.03–55.44) were independent factors for increased CA 19-9. The fitness of this model was confirmed with the Hosmer-Lemeshow GOF test (p=0.700) (Table 3).

Follow-up measurements of CA 19-9 concentrations and results of subsequent cancer screenings

Follow-up measurements of CA 19-9 concentrations were performed in 88 of 119 patients (73.9%) after median of 100 days (range: 8–980 days) following the initial measurements. Of these 88 patients, concentrations of CA 19-9 decreased to within the normal range in 58 (65.9%).

Of the 119 patients with increased CA 19-9 concentrations, cancer screening was repeated in 85 patients (71.4%) at 30 months (range: 6–60 months) after initial screening. Only one patient was diagnosed with cancer (hepatocellular carcinoma).

Discussion

It is recommended that CA 19-9 be measured every 1–3 months in patients with locally advanced or metastatic pancreatic cancer who are undergoing treatment (15). However, CA 19-9 may be increased in other malignancies such as ovarian cancer, colon cancer, and gastric cancer (16). In addition, CA 19-9 increases have been reported in various benign conditions such as Hashimoto's thyroiditis (16), benign biliopancreatic diseases (17), and several lung diseases (6–9). In the present study, 11 (8.5%) out of 130 participants with increased CA 19-9 had malignancy; only five of which had pancreatic cancer. This observation suggests that the specificity of increased CA 19-9 for the presence of pancreatic cancer is very low. In addition, the transient elevations in CA 19-9 that we observed in two-thirds of patients weakens the rationale of using CA 19-9 for cancer screening.

In addition, 68 (57.1%) of the 119 participants with increased CA 19-9 concentrations had various pulmonary radiographic abnormalities but no malignant diseases. In a logistic regression model, an increased ESR and HbA_{1c}, and the presence of bronchiectasis, bronchiolitis, emphysema, and interstitial fibrosis were associated with higher concentration of CA 19-9.

The mechanism responsible for increased CA 19-9 in pulmonary abnormalities is yet to be defined. However, the presence of inflammatory processes in bronchiectasis, bronchiolitis, interstitial fibrosis, and emphysema could help mediate higher CA 19-9 concentrations. In fact, other benign diseases associated with increased CA 19-9 include pyogenic liver abscess (18), diverticulitis (19), lumbar abscess (20), pelvic inflammatory disease (21), Hashimoto's thyroiditis (16), and connective tissue diseases including rheumatoid arthritis (22). These observations suggest that increased CA 19-9 is possibly associated with inflammation. Our finding that an increased ESR was associated with an increased CA 19-9 concentrations further supports this idea. Furthermore, CA 19-9 along with other tumor markers was recently proposed as an adhesion molecule in synovial inflammation (23).

Some reports indicate increased CA 19-9 in patients with diabetes (24, 25). In addition, a corresponding change in CA 19-9 with HbA_{1c} in patients with diabetes has also been reported (26). This proposed relationship between HbA_{1c} and CA 19-9 is supported by our study. Given that the inflammatory processes are important in etiology (27) as well as in complications of diabetes (28), these findings could be mediated through inflammation.

To properly appreciate these results, we note some limitations of our study. First, the diagnoses of pulmonary abnormalities were based on LDCT findings without consideration of clinical symptoms and pulmonary function. Differences might have been identified if clinical diagnoses of various lung diseases were used along with radiographic features. Second, the study population did not reflect the general population. The people participating in the cancer screening program tended to be wealthier and more concerned about their health. Prospective studies involving people with diverse economic circumstances and including detailed clinical findings and pulmonary functions should be undertaken in the future.

In conclusion, increased ESR and HbA_{1c}, in addition to various radiographic lung abnormalities, constitute

the majority of benign conditions associated with an increased serum CA 19-9 concentration. Clinicians should interpret CA 19-9 concentrations in patients with these clinical conditions with caution.

Conflict of interest

None of the authors has a conflict of interest to be declared.

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