Serum Levels of CA19-9 in Patients With Nonmalignant Respiratory Diseases

Takahide Kodama, Hiroaki Satoh,* Hiroichi Ishikawa, and Morio Ohtsuka

Division of Respiratory Medicine, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

CA19-9 is a specific tumor marker in patients with gastrointestinal cancer; however, some patients with respiratory disease can have elevated serum levels of CA19-9 as well. In this study we evaluated serum CA19-9 levels of patients with nonmalignant respiratory diseases. We also estimated the prognostic significance of elevated serum levels of CA19-9 in patients with interstitial lung diseases. The study included 554 patients who had been diagnosed at our hospital during the period of 1984–2005. Serum CA19-9 levels in these patients were measured with a commercially available kit. Elevated levels (>37 U/mL) of CA19-9 were observed in 30.7% of patients with lung cancer. Furthermore, 38.9% of patients with idiopathic

interstitial pneumonia (IIP), collagen disease-associated pulmonary fibrosis (CDPF), diffuse panbronchiolitis (DPB), and bronchiectasis had elevated serum CA19-9 levels. Survival rates were significantly lower in patients with interstitial lung diseases (IIP and CDPF) and elevated serum CA19-9 levels than in those with levels in the normal range ($P = 0.0065$). Serum CA19-9 was elevated in some patients with nonmalignant diffuse lung diseases. Therefore, clinicians should pay attention to the evidence that increased serum CA19-9 levels can be found in nonmalignant respiratory disease patients. In patients with IIP and CDPF, elevated serum CA19-9 levels may be related to poor prognosis. *J. Clin. Lab. Anal.* 21:103–106, 2007. © 2007 Wiley-Liss, Inc.

Key words: CA19-9; respiratory diseases; lung cancer; idiopathic interstitial pneumonia; collagen diseases; lung fibrosis; prognosis

INTRODUCTION

Serum CA19-9 levels have been established as a useful tumor marker for gastrointestinal cancers, especially biliary tract and pancreas cancers (1–3). The CA 19-9 assay detects a mucin containing the sialated Lewis-a pentasaccharide epitope, fucopentose II (4,5). Based on the average concentration of CA19-9 in sera from healthy individuals and those from patients with adenocarcinomas, the manufacturer's recommended cutoff level was determined to be <37 U/mL (6). However, elevated serum levels of CA19-9 can also be observed in various nonmalignant gastrointestinal diseases (7). Furthermore, investigators have reported elevated serum levels of CA19-9 in patients with nonmalignant respiratory diseases, such as idiopathic interstitial pneumonia (IIP) (8–11) and diffuse panbronchiolitis (DPB) (12), without malignant disease in any sites. It is possible that gastrointestinal cancers develop in patients with nonmalignant respiratory disease; however, the influence of respiratory comorbid disease on serum CA19-9 levels has not been fully investigated.

In the present study we evaluated the evidence that increased serum CA19-9 levels can occur in patients with nonmalignant respiratory disease. In addition to this, we estimated the prognostic significance of elevated serum levels of CA19-9 in patients with IIP and collagen disease-related pulmonary fibrosis (CDPF).

MATERIALS AND METHODS

Subjects

We studied 554 patients from the University of Tsukuba Hospital who had been diagnosed with nonmalignant respiratory diseases and lung cancer during the period of 1984–2005. Patients who had a nonmalignant respiratory disease or a synchronous

*Correspondence to: Hiroaki Satoh, Division of Respiratory Medicine, Institute of Clinical Medicine, University of Tsukuba, Tennodai 1-1-1, Tsukuba, Ibaraki, 305-8575, Japan.

E-mail: hiroasato@md.tsukuba.ac.jp

Received 27 July 2006; Accepted 31 August 2006

DOI 10.1002/jcla.20136

Published online in Wiley InterScience (www.interscience.wiley.com).

malignant disease other than lung disease, or developed a malignant disease during the study were not included in this study.

The diagnosis of IIP was made on clinical, radiological, physiological, and histological grounds (13). The criteria used included the following: history of exertional dyspnea and cough; fine crackles on physical examination; compatible findings on chest radiography; physiologic abnormalities of restrictive lung defects, including decreased diffusing capacity; and abnormal arterial oxygen tension. The patients with CDPF were clinically classified as having rheumatoid arthritis, polymyositis and dermatomyositis, Sjögren syndrome, systemic sclerosis, and mixed connective tissue disease using the criteria for each disease (14–19). Eighteen patients with IIP and CDPF died of progressive respiratory failure during the study period.

The lung cancers were comprised of 272 non-small-cell carcinomas and 51 small-cell carcinomas. Patients with lung cancer were classified according to the TNM staging system (20) before any treatment was given. Forty-six patients had stage IA-B, 15 patients had stage IIA-B, 114 patients had stage IIA-B, and 148 patients had stage IV disease.

Twenty normal control subjects (14 men and six women, average age = 50 years) were also studied. Six of the subjects were smokers. These subjects had no history of lung disease, no clinical findings suggestive of lung disease, and normal renal and liver function.

Peripheral venous blood samples were obtained and centrifuged at 1,000 *g* for 10 min at 4°C. The serum was frozen and stored at –30°C.

Measurement of CA19-9 Levels

Serum CA19-9 levels were measured with an enzyme immunoradiometric assay kit (Centocore, New York, NY). The assay was performed by technicians who had no clinical information regarding the samples. Serum CA19-9 levels were considered to be elevated when they were >37 U/mL (6).

Statistical Methods

The Mann-Whitney *U*-test was applied to elucidate the difference between two independent groups, and the proportion was compared by means of the chi-squared test. To determine the most suitable cutoff level, we used the receiver operating characteristic (ROC) curve analysis (21). The Kaplan-Meier method was used to assess survival curves, and a log-rank test was used to evaluate the statistical significance of differences found between the two groups ($P < 0.05$ was considered significant).

RESULTS

During the study period, serum levels of CA19-9 were evaluated in 554 patients with nonmalignant respiratory disease and lung cancer. Of these 554 patients, 231 had nonmalignant respiratory diseases and 323 had primary lung cancer (Table 1).

Serum Levels of CA19-9

The median serum levels of CA19-9 in the healthy control group were 11 U/mL (interquartile range: 9–15 U/mL). No healthy subjects showed elevated serum levels of CA19-9 >37 U/mL. The serum levels were elevated (>37 U/mL) in 42 of the 231 patients (18.2%) with nonmalignant respiratory diseases. The 50th, 75th, 90th, and 95th percentile serum CA19-9 levels were 16, 29, 73, and 136 U/mL, respectively.

CA19-9 levels in patients with IIP ranged from 6 to 3267 U/mL (median: 28 U/mL, interquartile range: 11–119 U/mL). CA19-9 levels in patients with CDPF ranged from 6 to 305 U/mL (median: 41 U/mL; interquartile range: 9–108 U/mL). There was no statistical difference in the levels of CA19-9 between IIP and CDPF ($P = 0.9684$). CA19-9 levels in patients with lung cancer ranged from 5 to 234,883 U/mL (median: 19 U/mL; interquartile range: 9–53 U/mL). As shown Table 1, the ratio of patients with >37 U/mL of serum CA19-9 was 36.7% in IIP, 55.0% in CDPF, 32.4% in bronchiectasis, 33.3% in DPB, and 60.0% in sarcoidosis. No elevated serum CA19-9 levels were found patients with tuberculosis, bronchial asthma, bronchitis, or hypersensitivity

TABLE 1. Serum CA19-9 levels in patients with benign respiratory diseases and lung cancer

Diagnosis	Patients, No.	CA19-9 > 37 U/mL	
		Positive rate, %	Range, U/mL
IIP	30	36.7	6–3267
CDPF	20	55.0	6–315
Pneumonia	48	6.3	5–60
Bronchiectasis	34	32.4	5–480
Tuberculosis	13	0	5–37
COPD	12	8.3	5–67
Bronchial asthma	35	0	5–35
DPB	6	33.3	10–105
Sarcoidosis	5	60.0	11–73
Bronchitis	20	0	5–34
Hypersensitivity pneumonia	4	0	12–24
Others	4	0	5–25
Lung cancer	323	30.7	5–234883

IIP: idiopathic interstitial pneumonia, CDPF: collagen disease-related pulmonary fibrosis, COPD: chronic obstructive pulmonary disease, DPB: diffuse panbronchiolitis.

TABLE 2. Demographic characteristics of the patients with IIP and CDPF*

Characteristics	Patients with Lower CA19-9 ($37 \leq \text{U/mL}$)	Patients with higher CA19-9 ($37 > \text{U/mL}$)	p-value
No. of patients	28	22	
Age, yr	60.5 ± 12.0	60.0 ± 10.1	0.8295
Male/female gender, No.	13/15	7/15	0.3869
IIP/CDPF, No.	19/9	11/11	0.2514
Patients who died during The study period, No.	6	12	0.0202

IIP: idiopathic interstitial pneumonia, CDPF: collagen disease-related pulmonary fibrosis.

*Data are presented as mean $\pm$ SD unless otherwise indicated.

pneumonia. On the other hand, elevated serum CA19-9 levels were observed in 30.7% of patients with lung cancer.

CA19-9 and Clinical Features in Patients With IIP and CDPF

The correlation between serum CA19-9 levels and various clinical features, including age, male/female ratio, smoking habit, IIP/CDPF ratio, and number of patients who died during the study period, are shown in Table 2. There were no significant differences concerning those factors between the patients with higher CA19-9 levels ($> 37 \text{ U/mL}$) and those with lower CA19-9 levels ($\leq 37 \text{ U/mL}$), except for the number of patients who died during the study period ($P = 0.0202$, χ^2 test). The patients with IIP and CDPF were followed up throughout the study period. The survival curves of 50 patients with these two diseases are shown in Fig. 1. There was a significant difference in survival rate between the two groups of patients based on serum CA19-9 levels ($P = 0.0065$, log-rank test).

To better define the ability of elevated level of CA19-9 in patients with IIP and CDPF to predict the likelihood of death, during the follow-up we performed an ROC curve analysis. We examined the sensitivity and specificity of various cutoff values of serum CA19-9 for predicting survival. On the basis of the ROC analysis, the optimum points on the ROC curves for discriminating between survivors and nonsurvivors corresponded to CA19-9; 85 U/mL.

DISCUSSION

In the present study, elevated serum CA19-9 levels were observed in 30.7% of patients with primary lung cancer, and serum CA19-9 levels were abnormally increased in only 5.0% of 141 patients with nonmalignant respiratory diseases other than IIP, CDPF, DPB, and bronchiectasis. However, elevated serum CA19-9

Fig. 1. Survival curves of two groups of patients with IIP and CDPF. The upper line is the survival curve of patients with CA19-9 levels $\leq 37 \text{ U/mL}$; the lower line is the curve of patients with CA19-9 levels $> 37 \text{ U/mL}$.

levels were observed in 38.9% of cases with these four nonmalignant diffuse lung diseases. CA19-9 has been used as a tool for the clinical detection of gastrointestinal cancers (3–5), and our results suggest that we should pay attention to the evidence that increased CA19-9 levels are found in patients with these nonmalignant diffuse lung diseases.

In previous studies that used immunohistochemical staining, CA19-9 was reported to be selectively expressed in regenerating epithelial cells in patients with IIP and DPB, regardless of the etiology (8,12). Therefore, the increased serum levels of CA19-9 may not be specific to patients with IIP and DPB. Together with our results, these findings indicate that increased CA19-9 levels can be observed in nonmalignant diffuse lung diseases when extensive regeneration of epithelial cells occurs in severely damaged lungs without developing lung cancer.

In the present study we also examined the relation between CA19-9 levels and the survival of the patients with IIP and CDPF. The patients with higher CA19-9 levels ($> 37 \text{ U/mL}$) showed a worse survival rate compared to those with lower CA19-9 levels ($\leq 37 \text{ U/mL}$). Why are the serum levels of CA19-9 related to the survival of the patients with IIP and CDPF? Previous immunohistochemical studies indicated that the source of the elevated serum CA19-9 may be regenerating epithelial cells associated with inflammatory changes in the peripheral lungs (8,12). The regenerating epithelial cells are thought to serve as repair cells that respond to peripheral lung damage resulting from various causes, and areas of epithelial regeneration may be closely related to the extent of fibrotic change as well as the degree of disease activity (8,12). In addition, some investigators reported that high levels of CA19-9 were present in the bronchoalveolar lavage (BAL) fluid of

patients with chronic airway inflammatory diseases, and that CA19-9 in serum and BAL fluid may be a useful marker to prove the existence of epithelial cell damage (9–12,22–25). However, serum levels of CA19-9 were not increased in all patients with IIP and CDPF. This may be because extensive regeneration of the epithelial cells did not always occur in the severely damaged lungs. Clinical features or pulmonary functions were influenced by morphologic remodeling of the lungs resulting from interstitial and alveolar fibrosis. The epithelial regeneration in the damaged lungs was variable in degree, although it was to a certain degree related to the extent of destruction. Therefore, in nonmalignant diffuse lung disease, such as IIP and CDPF, serum levels of CA19-9 can indicate the degree of disease activity (i.e., elevated CA19-9 levels can indicate diffuse pulmonary destruction as well as epithelial regeneration). Therefore, we consider that elevated serum CA19-9 levels may be related to the poor survival of these patients. It is possible that this also applies to patients with other diffuse lung diseases, such as bronchiectasis and DPB, although we did not evaluate that in this study.

In conclusion, the present study reveals that serum levels of CA19-9, which have been used as a tumor marker in gastrointestinal cancers, were also elevated in some patients with nonmalignant diffuse lung diseases. Therefore, clinicians should pay attention to the evidence that increased serum CA19-9 levels are found in nonmalignant respiratory disease patients without cancer in any site. Our results also show that survival rates were significantly lower in patients with IIP and CDPF and elevated serum CA19-9 levels compared to those with CA19-9 levels in the normal range. The elevated serum levels of CA19-9 may indicate the degree of disease activity and a poor prognosis, especially in patients with IIP and CDPF.

REFERENCES

- Ho JJ, Bi N, Yan PS, et al. Characterization of new pancreatic cancer-reactive monoclonal antibodies directed against purified mucin. *Cancer Res* 1991;51:372–380.
- Safi F, Roscher R, Berger HG. The clinical relevance of the tumor marker CA 19-9 in the diagnosing and monitoring of pancreatic carcinoma. *Bull Cancer* 1990;77:83–91.
- Plebani M, Basso D, Panozzo MP, et al. Tumor markers in the diagnosis, monitoring and therapy of pancreatic cancer: state of the art. *Int J Biol Markers* 1995;10:189–199.
- Lamerz R. Role of tumour markers, cytogenetics. *Ann Oncol* 1999;10(Suppl 4):145–149.
- Magnani JL. The discovery, biology, and drug development of sialyl Lea and sialyl Lex. *Arch Biochem Biophys* 2004;426:122–131.
- Del Villano BC, Brennan S, Brock P, et al. Radioimmunometric assay for a monoclonal antibody-defined tumor marker, CA19-9. *Clin Chem* 1983;29:549–552.
- Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor K. The value of serum CA19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. *Dig Dis Sci* 2005;50:1734–1740.
- Shimizu Y, Hamada T, Tanaka Y, et al. Colonization of CA19-9 and KL-6 to epithelial cells in dilated bronchioles in a patient with idiopathic pulmonary fibrosis complicated by diffuse alveolar damage. *Respirology* 2002;7:281–284.
- Ishii H, Mukae H, Kadota J, et al. High serum concentrations of surfactant protein A in usual interstitial pneumonia compared with non-specific interstitial pneumonia. *Thorax* 2003;58:52–57.
- Obayashi Y, Fujita J, Nishiyama T, et al. Role of carbohydrate antigens sialyl Lewis(a)(CA19-9) in bronchoalveolar lavage in patients with pulmonary fibrosis. *Respiration* 2000;67:146–153.
- Tonami Y, Saito Y, Miyachi H, et al. Clinical characterization of CA19-9 in patients with interstitial pneumonia showing pathological nonspecific interstitial pneumonia pattern [in Japanese]. *Nohon Kokyuki Gakkai Zasshi* 2005;43:77–83.
- Mukae H, Hirota M, Kohno S, et al. Elevation of tumor-associated carbohydrate antigens in patients with diffuse pan-bronchiolitis. *Am Rev Respir Dis* 1993;148:744–751.
- American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–324.
- Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292:344–347.
- Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581–590.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
- Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–548.
- Kasukawa R, Tojo T, Miyawaki S, et al. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, editors. *Mixed connective tissue disease and anti-nuclear antibodies*. Amsterdam: Elsevier, 1987;41–47.
- Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710–1717.
- McNeil BJ, Keller E, Adelstein SJ. Primer on certain elements of decision making. *N Engl J Med* 1975;293:211–215.
- Totani Y, Demura Y, Ameshima S, et al. Serum CA19-9 levels reflect bronchoalveolar lavage fluid neutrophil levels in idiopathic pulmonary fibrosis. *Respiration* 2001;68:438.
- Yamazaki Y, Kubo K, Takamizawa A, et al. Markers indicating deterioration of pulmonary *Mycobacterium avium-intracellulare* infection. *Am J Respir Crit Care Med* 1999;160:1851–1855.
- Yamanouchi H, Fujita J, Yoshinouchi T, et al. Measurement of hepatocyte growth factor in serum and bronchoalveolar lavage fluid in patients with pulmonary fibrosis. *Respir Med* 1998;92:273–278.
- Gronowitz E, Pitkanen S, Kjellmer I, et al. Association between serum oncofetal antigens CA19-9 and CA125 and clinical status in patients with cystic fibrosis. *Acta Paediatr* 2003;92:1267–1271.