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Carbohydrate Antigen 19-9 (CA19-9) Represents the Disease Activity of Nontuberculous Mycobacteria

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Abstract

Pulmonary MAC disease causes pulmonary involvement, such as bronchiectasis and small nodules, particularly in the middle lobe and lingular segment. An evaluation of the efficacy of pulmonary MAC disease treatment is difficult. The investigation of biomarkers against MAC infection may lead to a more precise evaluation of the treatment for MAC infection. We experienced several cases of pulmonary MAC disease and found carbohydrate antigen 19-9 (CA19-9) concentrations correlated with the activity of pulmonary MAC disease. In this study, we evaluated the role of CA19-9 as a biomarker in pulmonary MAC disease. We found an elevation of CA19-9 during pulmonary MAC disease, but not in tuberculosis, suggesting a relationship between CA19-9 and the disease activity in the elevated CA19-9 group. CA19-9 may be a promising biomarker for the evaluation of the disease activity of pulmonary MAC disease.

Keywords: CA19-9; Mycobacteria; Biomarker

Introduction

Nontuberculous mycobacteria (NTM) cause chronic pulmonary involvement. *Mycobacterium avium*-intracellulare complex (MAC) comprises approximately 70% of NTM cases and *M. kansasii* comprises approximately 20%. MAC is an intracellular proliferating pathogen that causes chronic progressive respiratory infection as well as disseminated diseases in HIV patients [1,2]. Pulmonary MAC disease causes pulmonary involvement, such as bronchiectasis and small nodules, particularly in the middle lobe and lingular segment. Several reports have demonstrated a 59-92% response rate for a clarithromycin-containing regimen [3-5]. However, relapses after medical therapy with treatment regimens are common [6,7]. Some parts of the lung involvement are frequently resolved, whereas other parts are progressive. This phenomenon makes the evaluation of the treatment for MAC infection difficult. Determination of the disease progression or resolution is crucial for treatment. Thus, the investigation of biomarkers against MAC infection may lead to a more precise evaluation of the treatment for MAC infection.

Carbohydrate antigen 19-9 (CA19-9) is a widely used tumor marker for pancreas and bile duct cancers. CA19-9 was discovered in the serum of patients with colon cancer and pancreatic cancer [8]. While a high CA19-9 concentration is most commonly associated with pancreatic cancer, other cancers, such as colorectal, lung, and gall bladder cancers, can cause elevated levels. Additionally, high CA19-9 levels may be caused by non-cancerous conditions, such as gall stones, pancreatitis, cystic fibrosis, liver disease, and chronic lung diseases [9]. Kodama and colleagues have also reported that 38.9% of patients with idiopathic interstitial pneumonia (IIP), collagen disease-associated pulmonary fibrosis, diffuse panbronchiolitis (DPB), and bronchiectasis had elevated serum CA19-9 levels.

We herein report the close relationship between the activity of pulmonary MAC disease and the kinetics of CA19-9. Additionally, we measured the serum levels of CA19-9 in MAC patients and found a relationship between CA19-9 and the activity of pulmonary MAC disease.

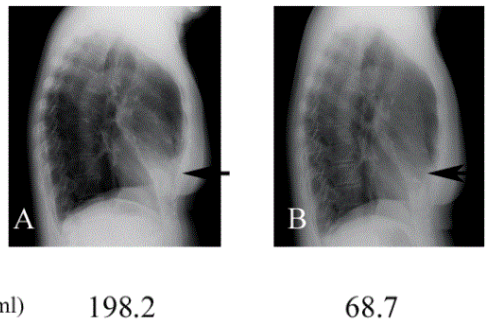

Figure 1: A representative case presentation of pulmonary MAC disease. Chest images were used for evaluation. *M. avium* infection provoked the middle lobe infiltration. (A) After treatment, the infiltration was partially resolved. (B) Additionally, the CA19-9 titer was 198.2 U/ml before treatment and 104.6 U/ml after treatment. Arrows indicate the infiltration.

Materials and Methods

Human sera analysis

We collected sera from 19 MAC patients before and after receiving treatment.The patient characteristics are summarized in Table 1. Each

patient's blood sample was measured using an enzyme immunoassay (SRL Inc, Tokyo). The assay was performed by technicians who were blinded to the clinical data of the samples. The normal range of CA19-9 is <37.0 U/ml.

Assessment of clinical course

Chest imaging using chest roentgenography or computer assisted tomography were evaluated. Apparent augmentation of infiltrates was defined as unfavorable outcome. Improvement of images was defined as favorable outcome.

Statistical analysis

The data were expressed as the mean ± standard error (SE). The Mann-Whitney U test was used to compare differences between the two groups. Statistical significance was considered to exist at $P<0.05$. Statistical analyses were performed using the StatView 5.0 software program.

Results

Case 1

A 64-year-old female was admitted to our hospital due to an elevation of the CA19-9 level (198.2 U/ml). She was carefully evaluated for malignancy; however, there was no evidence of malignancy. The chest images demonstrated bronchiectasis and small nodules in the middle lobes and left lingular segment. A repeat examination of the sputum and bronchofiberscopy revealed the presence of M. avium. She received treatment with rifampin, ethambutol and clarithromycin for 12 months. Subsequently, the sputum examination became negative for *M. avium*; however, it indicated left pulmonary involvement. We measured the CA19-9 level at the end of treatment and it had decreased to 68.7 U/ml. The case presentation is shown in Figure 1.

	Pulmonary MAC	Tuberculosis
Gender (M/F)	2/17	3/3
Age in years (median)	50-85 (61)	21-57 (46)
Avium/Intracellulare*	14/6	-

Table 1: The characteristics of the patients with pulmonary MAC disease and tuberculosis. *One patient with pulmonary MAC disease was infected with both *M. avium* and *M. intracellulare*.

Case 2

A 51-year-old female with rheumatoid arthritis treated with prednisolone was admitted to our hospital due to an elevation of the CA19-9 level (478 U/ml). She was carefully evaluated for malignancy; however, there was no evidence of malignancy. Bronchofiberscopy revealed the presence *M. avium*. She received treatment with rifampin, ethambutol and clarithromycin for 12 months and the resolution of the pulmonary development was achieved. At the end of the treatment, the patient's CA19-9 level decreased to 26 U/ml. Rheumatoid arthritis was stable during the period.

Case 3

A 67-year-old female was admitted to our hospital due to chest pain. She was diagnosed with pulmonary MAC disease and received treatment with rifampin, ethambutol and clarithromycin. Unfortunately, she stopped her treatment. At that time, the patient's CA19-9 level was 75 U/ml. Five years later, the patient complained of a productive cough. The chest image demonstrated the progression of the pulmonary development and the CA19-9 level was elevated (201 U/ml).

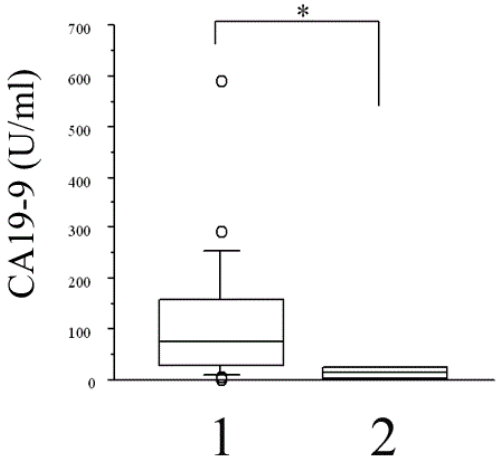

Figure 2: CA19-9 titer in pulmonary MAC disease and tuberculosis. The pulmonary MAC disease group demonstrated significantly higher titers of CA19-9 compared with the tuberculosis group ($P=0.0058$). Lane 1: pulmonary MAC disease group (N=19); Lane 2: pulmonary tuberculosis group (N=6).

According to these clinical cases, we speculated that CA19-9 may represent the disease activity of pulmonary MAC disease. We measured the CA19-9 level in 19 patients with pulmonary MAC diseases (Figure 2). The CA19-9 titer was higher in the MAC disease group than in the tuberculosis group (N=6).

We selected 8 patients in whom the clinical courses after treatment could be followed for at least two years. Six patients showed a favorable outcome, which meant improvement of chest images. However, two patients demonstrated deterioration of chest images. We compared the CA19-9 titers before and after treatment between the two groups (Figure 3). The CA19-9 titer was clearly decreased in the favorable outcome group after receiving treatment. On the contrary, the CA9-9 titer was elevated in the unfavorable outcome group, although the number of patients in this group was small.

Discussion

CA19-9 has been reported to be a good tumour marker for pancreatic cancer. Unfortunately, the evaluation of CA19-9 in the serum in pancreatic cancer patients is limited due to a poor sensitivity, false negative results in the Lewis negative phenotype (5-10%) and increased false positivity in the presence of obstructive jaundice (10-60%) [10]. Moreover, CA19-9 has been reported to be observed in lung diseases. Kim et al. reported that a higher erythrocyte

sedimentation rate, higher hemoglobin A1c, bronchiectasis, bronchiolitis, emphysema, and interstitial fibrosis were independent factors for increased CA19-9 [11]. Furthermore, other investigators have reported elevated serum levels of CA19-9 in patients with non-malignant respiratory diseases, such as IIP [12] and DPB [13]. CA19-9 was reported to be selectively expressed in regenerating epithelial cells in patients with IIP and DPB. The authors speculated that increased CA19-9 levels can be observed in non-malignant diffuse lung diseases following the extensive regeneration of epithelial cells in severely damaged lungs [12,13].

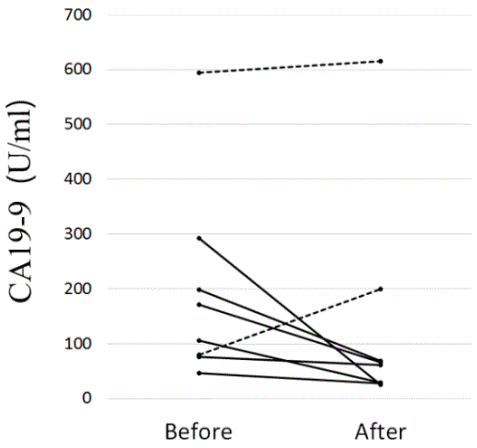

Figure 3: The CA19-9 titer profile in patients with pulmonary MAC disease before and after treatment. The CA19-9 titer was measured in the patients with pulmonary MAC before and after treatment. A favorable outcome means the improvement of chest images. An unfavorable outcome means the deterioration of chest images. A solid line indicates a favorable outcome (N=6), whereas a dashed line indicates an unfavorable outcome (N=2). In the favorable outcome group, all cases demonstrated a decrease in the CA19-9 titer, whereas in the unfavorable outcome group all cases showed an increase in the CA19-9 titer.

In this study, we demonstrated the association between CA19-9 and MAC disease activity. The CA19-9 titer decreased in cases 1 and 2 followed by the improvement of pulmonary MAC disease, and the CA19-9 level elevated with the progression of pulmonary MAC disease in case 3. We speculated that the CA19-9 titer changed along with the disease activity. Then, we evaluated the titer of CA19-9 in patients with pulmonary MAC disease and pulmonary tuberculosis. Fourteen patients (73.6%) with pulmonary MAC disease had CA19-9 titers higher than the cut off value (37 U/ml). On the contrary, none of the patients in the pulmonary tuberculosis group had elevated CA19-9 titers. However, the relationship between CA19-9 and tuberculosis has been reported in several reports [14]. Regarding pulmonary MAC disease, CA19-9 in BAL fluids has been reported to be significantly elevated in the deteriorated group [15]. These reports, and the results in the present study, indicated that pulmonary mycobacteriosis is related to the elevation of CA19-9. Careful attention is necessary in the patients with elevated CA19-9 titers and pulmonary involvement.

It is often difficult to evaluate the response to treatment during pulmonary MAC disease. Many patients are incapable of producing sputum, and the time course and the evaluation of chest roentogenography may be difficult. If a serum diagnostic test is capable of aiding in the diagnosis of MAC, then it may be useful for following the disease activity. Several trials were investigated to find a biomarker of pulmonary MAC diseases [15,16]. Plasma beta-defensin (HBD)-2 levels in NTM patients before treatment were reported to be higher than those in the controls, while the HBD-1 levels in the NTM patients were similar to the control levels [17].However, there was no relationship observed between the HBD levels and disease activity. Recently, the glycophospholipid (GPL) of MAC antibody was used as a marker for the diagnosis of MAC [18]. GPLs are the major cell-surface antigens of slow-growing mycobacteria, such as MAC, whereas *M. kansasii*, *M. tuberculosis* complex and bacillus Calmette-Guerin (BCG) do not have GPLs in their cell walls [19]. Kitada and colleagues showed excellent results with a sensitivity of 92.5% and specificity of 95.1% for the GPL core [18]. However, the effects of treatment on the titers were limited because the anti-GPL core IgA antibody levels did not change with the failure of chemotherapy, and there was no conversion from seropositive status to seronegative status [20]. In this study, we followed the CA19-9 titer in the pulmonary MAC disease group before and after treatment. As shown in Figure 3, the CA19-9 titer correlated with the disease activity. In the future, this relationship should be confirmed with a larger sample size.

There are some limitations associated with this study. One limitation is the small number of patients. However, a clear tendency was observed in this study. Another factor is the role of Lewis antigen. Approximately 10% of Caucasian patients negative for Lewis antigen did not have an elevated CA19-9 titer [10]. Thus, the significance of CA19-9 is not indicated for all patients. One major issue is that this study included several cases of bronchiectasis. Bronchiectasis could cause the elevation of CA19-9. It is complicated relationship between bronchiectasis and pulmonary MAC disease. Pulmonary MAC diseases result in bronchiectasis, and while on the other hand, pulmonary MAC diseases results from bronchiectasis. It is difficult to exclude the effect of bronchiectasis on the elevation of CA19-9. However, activity of pulmonary MAC diseases is apparently associated with CA19-9 level. Moreover, bronchiectasis did not progress during the period. Another major limitation is the lack of a mechanism for why the CA19-9 titer was elevated in the patients with MAC disease. We suspected that inflammation around the bronchiole may be critical. In addition, the expression of CA19-9 was reported in the bronchial epithelium (12,13). The infiltration of inflammatory cells during pulmonary MAC disease may stimulate the production of CA19-9. Moreover, whether the elevation of CA19-9 is due to pulmonary MAC disease per se or bronchiectasis by pulmonary MAC diseases is unclear. Thus, the mechanism of the elevated CA19-9 titer during MAC diseases must be clarified.

In conclusion, we herein found an elevation of CA19-9 in patients with pulmonary MAC disease, but not in patients with tuberculosis, and a relationship between the CA19-9 level and the disease activity in the patients with MAC disease. CA19-9 may be a promising marker for the evaluation of the disease activity of pulmonary MAC disease.

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