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Elevated serum CA 19-9 levels in patients with pulmonary nontuberculous mycobacterial disease

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ABSTRACT

Increased serum CA 19-9 levels in patients with nonmalignant diseases have been investigated in previous reports. This study evaluates the clinical significance of serum CA 19-9 elevation in pulmonary nontuberculous mycobacterial disease and pulmonary tuberculosis. The median CA 19-9 level was higher in patients with pulmonary nontuberculous mycobacterial disease than in patients with pulmonary tuberculosis (pulmonary nontuberculous mycobacterial disease: 13.80, tuberculosis: 5.85, $p < 0.001$). A multivariate logistic regression analysis performed in this study showed that *Mycobacterium abscessus* (OR 9.97, 95% CI: 1.58, 62.80; $p = 0.014$) and active phase of pulmonary nontuberculous mycobacterial disease (OR 12.18, 95% CI: 1.07, 138.36, $p = 0.044$) were found to be risk factors for serum CA 19-9 elevation in pulmonary nontuberculous mycobacterial disease. The serum CA 19-9 levels showed a tendency to decrease during successful treatment of pulmonary nontuberculous mycobacterial disease but not in pulmonary tuberculosis. These findings suggest that CA 19-9 may be a useful marker for monitoring therapeutic responses in pulmonary nontuberculous mycobacterial disease, although it is not pulmonary nontuberculous mycobacterial disease-specific marker.

Introduction

Pulmonary nontuberculous mycobacterial (PNTM) disease appears to be increasing in many regions of the world, and the burden of PNTM is substantial.[1–4] In South Korea and other regions in which the incidence of tuberculosis (TB) is intermediate, differential diagnosis between PNTM and TB has become an important issue as nontuberculous mycobacteria (NTM) isolation from respiratory specimens has increased.[5,6]

In PNTM disease, there is a lack of known biomarkers associated with disease activity and therapeutic response. Diagnosis of PNTM disease is defined by clinical criteria, radiographic presentation, and microbiologic results. Additionally, the goal of the treatment of PNTM disease includes symptomatic, radiographic, and microbiologic improvement.

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However, sputum specimen is frequently not achievable in some patients; the symptom profile of PNTM disease varies, and subjective assessment of the clinician has often come into play. Thus, many clinicians rely on radiography including chest X-ray and high-resolution computed tomography (CT) scanning to assess the severity of PNTM disease[7] and for the monitoring of the treatment response. However, repeating CT scans increases cost and cumulative radiation dose. Thus, there is a need to identify biomarkers to estimate PNTM disease severity and to monitor treatment response.

Carbohydrate antigen 19-9 (CA 19-9) is a sialylated Lewis (Le) blood group antigen and a widely used tumor marker for epithelial type gastrointestinal cancers, especially pancreatic cancer.[8,9] However, elevated levels of CA 19-9 can also be detected in patients with nonmalignant diseases including pancreatic, liver, and biliary diseases.[10–12] In particular, there are several reports of increased serum CA 19-9 in several benign lung diseases including diffuse panbronchiolitis, emphysema, fibrosis, and bronchiectasis.[12–14]

A previous study reported that increased serum CA 19-9 levels may indicate clinical deterioration of PNTM disease[15] and some reports suggest that elevated CA 19-9 levels decreased after successful treatment of PNTM disease, contrary to pulmonary tuberculosis.[16–18]

The aim of this study was to investigate the clinical significance of serum CA 19-9 elevation in PNTM diseases. We evaluated the factors associated with CA 19-9 elevation in PNTM disease and compared the change of CA 19-9 levels as a result of treatment of patients with either PNTM disease or TB patients.

Materials and methods

Patients and data collection

A total of 59 patients with PNTM disease and 36 patients with pulmonary TB who visited Severance Hospital, a university-affiliated tertiary referral hospital in South Korea, between March 2011 and December 2013 were enrolled. All patients provided written informed consent before enrollment and this prospective study was approved by the Ethics Review Committee of Severance Hospital. Any patients with active cancer within five years based on medical chart review and interview were excluded.

PNTM disease was diagnosed based on the American Thoracic Society (ATS) guidelines.[19] Radiologic disease types of PNTM were categorized as nodular bronchiectatic (NB), fibrocavitary (FC), or mixed. Although the NB form was characterized with bronchiectasis and multiple centrilobular nodules, the FC form was defined as a fibrocavitary lesion on chest CT. The number of involved lobes was investigated as an indicator of radiological severity. NTM species were identified via a polymerase chain reaction (PCR)-restriction fragment length polymorphism method based on the *rpoB* gene.[6,20] Among 59 patients with PNTM disease, 24 patients were treated with anti-NTM regimens according to the ATS guidelines.[19] Active phase of PNTM disease was defined as present in patients with persisting positive microbiological cultures and clinical deterioration based on symptoms and radiographic findings, who was treated for PNTM disease or was advised to treat in six month.

Twenty-two patients with MAC (*Mycobacterium avium-intracellulare*) lung disease received a standardized antibiotic combination consisting of clarithromycin (1000 mg/day), rifampicin (450 mg for patients who were <50 kg or 600 mg for patients who were ≥50 kg), and ethambutol (25 mg/kg for two months, then 15 mg/kg/day).[19] Two patients with *M. abscessus* complex lung disease were treated with a standardized regimen consisting of intravenous cefoxitin (12 g/day), amikacin (10–15 mg/kg) and azithromycin (250 mg/day).[19] The treatment duration was usually 24 months including at least 12 months after sputum culture conversion.[21]

Response to anti-NTM treatment was defined as sputum culture conversion and radiographic improvement within 12 months of treatment. Culture conversion was defined as three consecutive negative sputum cultures from the date of the first negative culture after the start of anti-NTM treatment.[21]

The diagnosis of active pulmonary TB was based on positive respiratory specimen culture or the presence of caseating granulomas in lung tissue. Additionally, patients with negative mycobacterial culture but with high likelihood of active TB and overall good responses after TB treatment were included. TB patients who were lost to follow-up during anti-TB treatment period or had concomitant immunosuppressive diseases requiring therapy or clinical conditions (such as HIV infection, lymphoma) were excluded. Patients were classified as low or moderate/high risk according to the risk factors for relapse. The risk factors for relapse were as follows: (1) cavitary lesion on chest imaging at diagnosis and (2) positive sputum culture after two months of anti-TB treatment.[22] The risk groups were classified according to the number of risk factors for relapse: two risk factors in the high risk group; one risk factor in the moderate risk group; and no risk factor in low risk group.

Measurement of serum CA 19-9

Blood samples were separated via centrifugation and frozen immediately at −70 °C. Serum CA 19-9 levels were measured with an Analytics E 170 (Elecsys module) immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany) using the electrochemiluminescence immunoassay technique. The normal range was defined as <34 U/mL according to the manufacturer's instructions.

Serum C-reactive protein (CRP) was measured via Chemistry Autoanalyzer Hitachi 7600 (Hitachi Co., Japan) with Daiichi reagent (Daiichi-Hitachi) using the turbidoimmunometric assays (TIA) technique with the normal range defined as <0.30 mg/dL according to the manufacturer's instructions. Serum CA 19-9 was measured before treatment in all patients and also measured again after at least 12 months of treatment in 24 patients with PNTM disease and after the completion of treatment in all TB patients.

Statistical analysis

Categorical variables were analyzed using the χ^2 test and continuous variables were analyzed using the Mann–Whitney test. The non-parametric Wilcoxon signed-rank test was used