

Association between Serum Anti-glycopeptidolipid-core IgA Antibody Titers and Clinical Characteristics of Mycobacterium Avium Complex Pulmonary Disease

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Abstract

Mycobacterium avium complex pulmonary disease (MAC-PD) can be serologically diagnosed according to the presence of anti-glycopeptidolipid (GPL)-core IgA antibodies. However, few studies have examined the association between serum anti-GPL-core IgA antibody titers and the clinical characteristics of patients with MAC-PD. From April 2014 to June 2019, we determined the level of anti-GPL-core IgA antibodies in 489 MAC-PD patients at our institute. Of them, 89 patients fulfilled the criteria of the American Thoracic Society and the Infectious Diseases Society of America statement on the diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. These patients were divided into antibody-positive ($n = 59$) or -negative ($n = 30$) groups according to their serum anti-GPL-core IgA antibody results. Additionally, the positive antibody group was further divided into a strong positive group ($n = 27$) and a weak positive group ($n = 32$), and their clinical characteristics were retrospectively compared. Disease progression requiring treatment during the 12 months following diagnosis and extensive radiological findings were significantly abundant in the strong positive group compared with the weak positive group. Our findings revealed that serum anti-GPL-core IgA antibody titers are useful not only for diagnosing MAC-PD but also for predicting the risk of exacerbation.

Introduction

The number of patients with *Mycobacterium avium* complex pulmonary disease (MAC-PD) is increasing globally [1–6]. In particular, there is an increasing number of cases of women with MAC-PD with central granular shadows of the middle lobe of the lung. Therefore, knowledge pertaining to its diagnosis, treatment, and management is essential for respiratory physicians. MAC-PD is the most frequently occurring nontuberculous mycobacteria (NTM) pulmonary disease [7], and it is often encountered in clinical practice. MAC-PD may have poor airway symptoms, and because the causative bacteria are not always detected in sputum samples, bronchoscopy may be essential for diagnosis. Furthermore, it may be difficult to detect bacteria by bronchoscopy, and some patients are hesitant to undergo bronchoscopy. Additionally, because MAC exists universally in soil, natural water, and tap water, it is difficult to distinguish between colonization and contamination [8].

MAC-PD is unlikely in patients who have a single positive sputum culture during the initial evaluation [9–11], but the rate of MAC-PD can be as high as 98% in those with ≥ 2 positive sputum cultures [9]. Therefore, a diagnosis of MAC-PD should be made if MAC is identified at least twice in sputum samples or once in bronchial washings. However, although relatively advanced MAC-PD easily meets the diagnostic criteria, sputum collection is not possible with asymptomatic patients, and a long period is required for a definitive diagnosis. In such cases, the level of serum anti-glycopeptidolipid (GPL)-core IgA is used for diagnosis and has been utilized in clinical practice in Japan since August 2011. The GPL core is part of the GPL antigen, which is found on the surface of the cell walls of MAC but not of *Mycobacterium tuberculosis* or *Mycobacterium kansasii*. It can be detected in the serum of patients with MAC infection using commercially available serodiagnostic kits that measure the antibody level. Several studies have reported a sensitivity of 58.6–85% and a specificity of 96.9–100% [12–17]. The presence of

anti-GPL-core IgA antibody is useful as a tool for the auxiliary diagnosis of MAC-PD, but since it is only used for auxiliary diagnosis, there are few reports comparing the differences in antibody titers. Thus, we compared the clinical course of cases with antibody titers of ≥ 5.0 U/mL (strong positive), 0.7–5.0 U/mL (weak positive), and < 0.7 U/mL (negative).

Results

Table 1 shows the clinical characteristics of the 89 MAC-PD patients in our cohort, including the microbiological and radiological findings. Of them, two-thirds were positive for anti-GPL-core IgA antibodies. None of the patients were known to be seropositive for human immunodeficiency virus. The male sex, infection with *M. intracellulare*, a history of smoking, the presence of a cavitory lesion, a MAC-positive sputum smear, and the administration of medications for MAC during the year following diagnosis were reported in approximately one-fifth of patients, respectively. The median body mass index (BMI) was toward the lower range of normal, and the median number of abnormal lung zones was four. More than three-quarters of the patients had comorbidities (Table 1).

Table 1

Baseline characteristics of MAC-PD patients with anti-GPL-core IgA antibody measured (N= 89)

| Characteristic | Baseline value |
|---|--------------------|
| Age (years) | 75 (66–80) |
| Female (%) | 71 (79.8) |
| BMI (kg/m ²) | 19.1 (17.9–21.5) |
| TP (g/dL) | 7.4 (7.0–7.9) |
| ALB (g/dL) | 3.8 (3.15–4.05) |
| CRP (mg/dL) | 0.14 (0.04–1.21) |
| IgG(mg/dL) | 1380 (1,227–1,555) |
| IgE(IU/mL) | 70.8 (17.5–189.8) |
| Smoking history | 19 (21.3%) |
| Previous tuberculosis | 7 (7.9%) |
| Comorbidity | 69 (77.5%) |
| Bloody sputum | 13 (14.6%) |
| Positive MAC smear | 18 (20.2%) |
| <i>Mycobacterium intracellulare</i> | 17 (19.1%) |
| Cavitary lesion | 17 (19.1%) |
| Zones with radiological findings | 4 (3–4) |
| Anti-GPL-core IgA antibody(strong/weak/negative) | 27/32/30 |
| Received treatment for MAC within 1 year of diagnosis | 17 (19.1%) |
| Data are expressed as medians (interquartile range) or numbers (%). | |
| ALB, serum albumin; BMI, body mass index; CRP, serum C-reactive protein; GPL, glycopeptidolipid; MAC, <i>Mycobacterium avium</i> complex; MAC-PD, <i>Mycobacterium avium</i> complex pulmonary disease; TP, serum total protein | |

Regarding disease progression requiring treatment, extensive radiological findings were significantly abundant in the strong positive group compared with the weak positive group. Positive acid-fast bacilli (AFB) smears were significantly abundant in the strong positive group compared with the antibody-negative group. Those with weak positive antibody titers did not significantly differ from those in the antibody-negative group (Table 2).

Table 2
Comparison of patient characteristics by anti-GPL-core IgA antibody titers (N= 89)

| Characteristics | Strong positive (n= 27) | Weak positive (n= 32) | Negative (n = 30) | P-value [†] |
|---|-------------------------|-----------------------------|-------------------|----------------------|
| Age, years | 73 (62.5–77.5) | 77.5 (69.75–82.25) | 74 (67.5–79.0) | 0.20 |
| Sex (female, %) | 23 (85.2%) | 26 (81.3%) | 22 (73.3%) | 0.53 |
| BMI (kg/m ²) | 18.7 (17.2–19.8) | 20.5 (18.1–22.4) | 19.4 (16.6–21.0) | 0.13 |
| TP (g/dL) | 7.4 (6.9–7.9) | 7.5 (7.2–7.9) | 7.4 (6.9–7.8) | 0.80 |
| ALB (g/dL) | 3.7 (3.4–4.0) | 3.9 (3.6–4.2) | 3.6 (3.0–4.0) | 0.16 |
| CRP (mg/dL) | 0.09 (0.03–0.61) | 0.09 (0.03–0.90) | 0.29 (0.11–2.6) | 0.12 |
| IgG (mg/dL) | 1336 (1233–1507) | 1387 (1242–1437) | 1457 (1144–1609) | 0.66 |
| IgE (IU/mL) | 75.3 (19.9–194.9) | 37.4 (17.3–84) | 73.5 (20.0–293) | 0.52 |
| Smoking history | 6 (22.2%) | 3 (9.4%) | 10 (30.3%) | 0.07 |
| Previous tuberculosis | 1 (3.7%) | 3 (9.4%) | 3 (10.0%) | 0.63 |
| Comorbidity | 21 (77.8%) | 27 (84.4%) | 21 (70.0%) | 0.40 |
| Bloody sputum | 6 (22.2%) | 6 (18.8%) | 1 (3.3%) | 0.09 |
| Positive MAC smear | 11 (40.7%) [‡] | 6 (18.8%) | 1 (3.3%) | 0.002 [*] |
| <i>Mycobacterium intracellulare</i> | 2 (7.4%) | 9 (28.1%) | 6 (20.0%) | 0.13 |
| Cavitary lesion | 6 (22.2%) | 7 (21.9%) | 4 (13.3%) | 0.62 |
| Zones with radiological findings | 4 (3–5) | 3 (2–4) | 3 (2–4) | 0.03 [*] |
| Anti-GPL-core IgA antibody titers | 16 (9.5–32.1) | 2.1 (1.28–3.1) [‡] | ≤ 0.7 | < 0.001 [*] |
| Received treatment for MAC within 1 year of diagnosis | 10 (37.0%) | 4 (12.5%) | 3 (10.0%) | 0.02 [*] |
| Data are expressed as medians (interquartile range) or numbers (%). | | | | |
| ALB, serum albumin; BMI, body mass index; CRP, serum C-reactive protein; GPL, glycopeptidolipid; MAC, <i>Mycobacterium avium</i> complex; TP, serum total protein | | | | |

| Characteristics | Strong positive (n = 27) | Weak positive (n = 32) | Negative (n = 30) | P-value [†] |
|---|-----------------------------|---------------------------|-------------------|----------------------|
| †P-values are for all comparisons. | | | | |
| *P < 0.05. | | | | |
| ¶P < 0.05 for anti-GPL-core IgA antibody weak titers vs. anti-GPL-core IgA antibody-negative. | | | | |
| ‡P < 0.05 for anti-GPL-core IgA antibody strong titers vs. anti-GPL-core IgA antibody-negative. | | | | |

Discussion

To our knowledge, this is the first report to describe the differences in clinical characteristics using an anti-GPL-core antibody titer threshold value of 5.0 U/mL. We set the threshold of the antibody-positive group to 5.0 U/mL, according to a previous report where the mean antibody titer that was considered the most reliable for MAC-PD diagnosis via bronchoscopy was 5.0 U/mL [18]. Among the antibody-positive MAC-PD patients in our study, the median value of anti-MAC antibodies was 4.5 U/mL, but considering the application to actual clinical practice and an objective evaluation, we selected 5.0 U/mL as the threshold between the strong positive and weak positive groups in our study.

In our study, 66.3% of the patients newly diagnosed with MAC-PD were positive for anti-GPL-core IgA antibodies, which is comparable to the sensitivity reported in a previous review [19]. Furthermore, the clinical characteristics of the patients with MAC-PD in our study were consistent with those in previous reports (i.e., the patients were predominantly slim women with nodular bronchiectatic disease) [1–6, 8, 20, 21].

Kitada *et al.* reported that the antibody titers reflect the disease activity to some extent [13, 22, 23] and found a weak correlation between the antibody levels and the extent of the disease on chest computed tomography (CT) [12, 24]. Similarly, we found that both disease progression requiring treatment and extensive radiological findings were significantly abundant in the strong positive antibody group in our study cohort. However, there was no significant difference in the presence or absence of cavitory lesions. Thus, a strong positive anti-GPL-core IgA antibody result was associated with higher radiological scores for infiltration, although no difference was observed in cavitory lesions between patients with strong positive and weak positive results. This correlates with another study showing that the anti-GPL-core IgA antibody titer was not associated with the extent of disease in the fibrocavitory disease phenotype [22].

We found that a positive AFB smear in the strong positive group was significantly more abundant than in the antibody-negative group and slightly more abundant than in the weak positive group ($P = 0.053$). Extensive radiological findings [23, 25] and an AFB-positive sputum smear [8, 25, 26] have been reported as exacerbating factors of MAC-PD, which increases the likelihood that a high antibody titer is an exacerbating factor.

However, the anti-GPL-core IgA antibody titer in patients with severe MAC-PD was sometimes low in our study, probably due to differences in individual immunity and immune response ability, but no significant difference was found in serum total protein, serum albumin, IgG, and IgE levels in our study. A lower BMI was considered an exacerbating factor in MAC-PD patients in previous studies [27, 28]. In our study, although many patients with MAC-PD were thin on average, there was no significant difference in BMI between the three groups.

In our study, *M. intracellulare* was found in 18.6% of patients with MAC-PD, and the infection rate was similar to other reports in Japan [29]. Regarding MAC species differentiation, some studies reported that patients with *M. intracellulare* infection experienced more frequent exacerbations than those with *M. avium* infection [30], but others reported that patients with *M. intracellulare* infection experienced a lower rate of recurrence than those with *M. avium* infection [31]. Thus, the difference in the prognosis between *M. avium* and *M. intracellulare* infections remains uncertain. In our study, there was no significant relationship between the prognosis and the MAC species in all three groups. Additionally, there was no significant difference in clinical features between the MAC-PD patients with weak positive anti-GPL-core IgA antibodies and those who were antibody-negative. Thus, MAC-PD patients with weak positive antibody titers were considered to be of no clinical importance in our study other than in the diagnostic method that was used.

Limitations

Our study has several limitations. First, because the sample size was small, the number of MAC-PD patients may have been underestimated since patients who were not diagnosed according to the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) guidelines were excluded from the analyses. Therefore, in reality, factors with clinical significance may have proven insignificant in the analyses due to reduced statistical power. Second, because data collection was retrospective, sputum cultures, laboratory data, and CT scans were performed according to clinical practice rather than according to strict schedules. Finally, the timing of the treatment was dependent on the decision of the attending physician.

Conclusions

Our study shows that anti-GPL-core IgA antibody titers > 5.0 U/mL can be used to both diagnose MAC-PD and to predict the risk of exacerbation. However, patients with weak positive antibody titers are not considered clinically significant other than in diagnostic methods. Although the anti-GPL-core IgA antibody is a qualitative test for MAC-PD, it can be useful as a quantitative test for MAC-PD severity.

Methods

Study Population and Design

We retrospectively reviewed all patients seen in our hospital in Tokyo, Japan, from April 2014 to June 2019. There were 481 patients who underwent serologic testing for anti-GPL-core IgA antibodies. Of them, 119 newly diagnosed NTM-PD patients fulfilled the criteria of the ATS and the IDSA statement on the diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases [8, 26]. Those with a past history of NTM disease, NTM other than MAC, and no abnormal shadow on chest CT were excluded, and the remaining 89 MAC-PD patients were enrolled in our study (Fig. 1). We divided the study patients into two groups according to anti-GPL-core IgA antibody results: an antibody-positive group ($n = 59$) and an antibody-negative group ($n = 30$, antibody titer <0.7 U/mL). Then, the antibody-positive group was further divided into a strong positive group ($n = 27$, antibody titer ≥ 5 U/mL) and a weak positive group ($n = 32$, $5.0 < \text{antibody titer} \leq 0.7$ U/mL). The antibody titers and the clinical characteristics of the patients, including age, sex, laboratory data, a past history of tuberculosis, comorbidities, and radiological findings, were retrospectively compared. Additionally, we investigated whether treatment was required for up to 1 year after diagnosis to determine if anti-GPL-core IgA antibody titers were associated with disease progression.

Ethics Approval and Consent to Participate

All methods were carried out in accordance with the declaration of Helsinki. The need of informed consent was waived by the Ethics Committee of Toho University Ohashi Medical Center due to the retrospective nature of the study. All protocols were approved by the Ethics Committee of Toho University Ohashi Medical Center (approval no. H20004).

Serological Determination of Anti-GPL-core IgA Antibody Titers

The titer of serum anti-GPL-core IgA antibodies was determined using a Capilia MAC Ab ELISA serodiagnostic kit (TAUNS Laboratories, Inc., Shizuoka, Japan). The cutoff value was defined as 0.7 U/mL, according to the manufacturer's instructions [22]. The test can be performed using a small amount of serum, and the turnaround time is approximately 4 hours [32].

Microbiological Examination

AFB were cultured in mycobacteria growth indicator tubes using sputum samples or bronchial washings obtained by bronchoscopy. The sputum samples were obtained on two or more occasions after the initial presentation. The diagnosis of MAC-PD was made when MAC was identified in sputum at least twice or once in bronchial washings. MAC was confirmed when cultures were positive for AFB, and the cultured AFB were subsequently confirmed as MAC by polymerase chain reaction.

Radiological Examination and Measurements

High-resolution chest CT findings were classified as either showing or not showing a cavitory lesion. Additionally, chest CT findings at the time of initial diagnosis were scored, as previously described [33]. Briefly, the lung fields were divided into six lobes based on anatomical structures: right upper, right middle, right lower, left upper (S1+2 and S3), left lingular (S4 and S5), and left lower lobes. We assessed whether, at the time of diagnosis, each lung lobe had a shadow, such as cavities, bronchiectasis, small nodules, consolidations, or atelectasis.

Statistical Analysis

The patients' characteristics are presented as medians (interquartile range). Numerical data are expressed as numbers (%). Intergroup differences (anti-GPL-core IgA antibody strong positive group vs. weak positive group vs. negative group) were compared using the Kruskal–Wallis test for numerical variables and the chi-square test or Fisher exact test for categorical variables where appropriate. All analyses were performed using SPSS Statistical software v22.0 (IBM Japan, Tokyo, Japan). *P*-values < 0.05 were considered significant.

Declarations

Author contributions

N.K. collected the data, analyzed the data, created the tables, designed the study, and wrote the manuscript. C.N., T.O., K.W., K.N., C.I., N.S., H.Mo., and H.Ma. collected the data. H.Ma. critically revised the manuscript. All authors read and approved the final manuscript.

Additional information

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

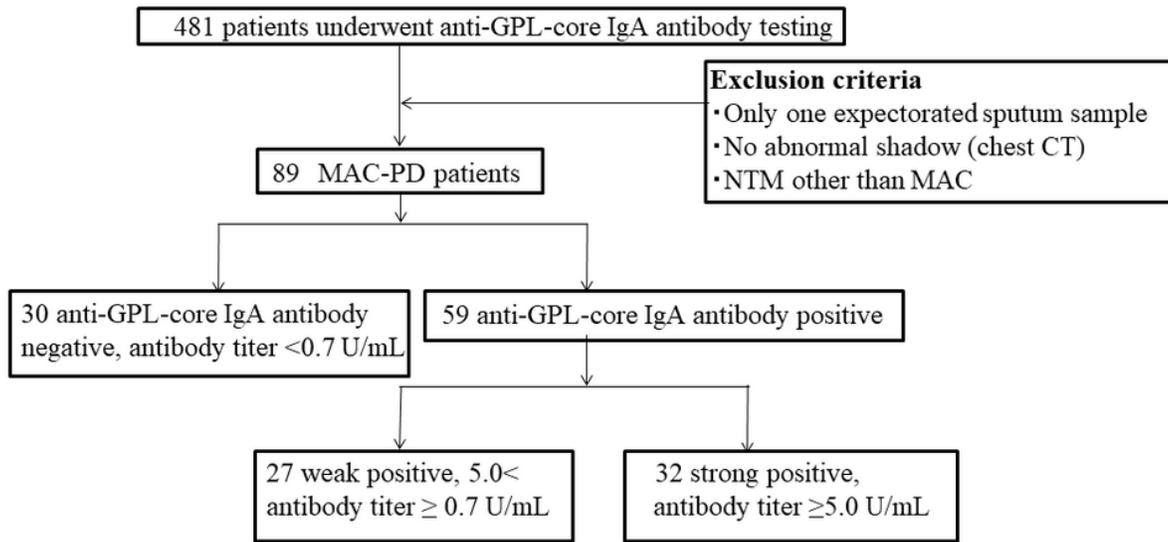


Figure 1

Flow chart of patients diagnosed with MAC pulmonary disease between April 2014 and June 2019 at our institution. MAC-PD, Mycobacterium avium complex pulmonary disease; CT, computed tomography; NTM, nontuberculous mycobacteria; MAC, Mycobacterium avium complex; GPL, glycopeptidolipid