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Prognosis of chronic pulmonary aspergillosis in patients with pulmonary non-tuberculous mycobacterial disease

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ABSTRACT

Background: Pulmonary non-tuberculous mycobacterial disease (PNTM) is a known risk factor for chronic pulmonary aspergillosis (CPA). However, few studies have focused on the prognosis of PNTM-associated CPA. In the present investigation, we aimed to elucidate the clinical course and prognostic factors of CPA in patients with PNTM.

Methods: We retrospectively investigated the medical records of 62 patients with CPA and a history of PNTM who were admitted to Kinki-chuo Chest Medical Center between 2010 and 2015. Co-morbidities, causative microorganisms, radiological findings, and outcomes were evaluated.

Results: The patients' median age was 69.5 years, and the median follow-up period was 4.2 years. The major underlying diseases, other than PNTM and CPA, were old pulmonary tuberculosis, chronic obstructive pulmonary disease, and interstitial pneumonia. The most common causative NTM species were *Mycobacterium avium* complex (MAC; 37 patients; 59.7%) and *Mycobacterium kansasii* (20 patients; 32.3%). Survival was 83% after 1 year and 61% after 5 years. Use of systemic corticosteroids (hazard ratio: 3.32, 95% confidence interval: 1.23–9.51; $P=0.00177$) and C-reactive protein levels $\geq$ 5.0 mg/dL (hazard ratio: 8.96, 95% confidence interval: 2.15–62.9; $P=0.0014$) at the time of CPA diagnosis were associated

Abbreviations: CAM, clarithromycin; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; CRP, C-reactive protein; CT, computed tomography; EB, ethambutol; FC, fibrocavitary; HR, hazard ratio; ILD, interstitial lung disease; INH, isoniazid; LVFX, levofloxacin; MAC, *Mycobacterium avium* complex; NB, nodular/bronchiectatic; NTM, non-tuberculous mycobacteria; PNTM, pulmonary nontuberculous mycobacterial disease; RFP, rifampin; SM, streptomycin; STFX, sitafloxacin; TB, tuberculosis

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with increased over-all mortality.

Conclusions: CPA frequently developed in patients with MAC and *M. kansasii* PNTM. The treatment course of PNTM was not associated with all-cause mortality. However, systemic corticosteroid use and high CRP levels were negative prognostic factors of CPA in patients with PNTM. Since the prognosis is poor, early diagnosis and treatment of CPA are important in patients with PNTM.

1. Introduction

Non-tuberculous mycobacteria (NTM) are found ubiquitously in natural and tap water, biofilms, soil, dust, and animals [1,2]. In the past few decades, the incidence of pulmonary NTM disease (PNTM) has increased worldwide—both in patients with a chronic lung disease or immunodeficiency and in those without any recognized underlying disorder, particularly elderly women [3]. *Aspergillus* species are also widespread in the environment; they cause chronic progressive pulmonary infection in individuals with a previous or underlying pulmonary disease [4–6]. In particular, PNTM increases the risk of chronic pulmonary aspergillosis (CPA) [7,8], which is referred to as chronic progressive pulmonary aspergillosis in Japan [9], and patients with PNTM-associated CPA show poor prognosis [10–12].

Several studies have focused on CPA and PNTM. However, various problems remain regarding diagnosis and treatment of CPA in patients with PNTM, including treatment priority of the diseases, evaluation of mixed radiological findings, and interactions of antimicrobial agents. Moreover, the prognosis in co-infected patients remains unknown.

Herein, we report a series of 62 patients from a single respiratory center who developed CPA after PNTM. The aim of the present study was to investigate the prognoses of, and correlations between, CPA and PNTM. In addition, we determined which factors are associated with mortality risk in these patients.

2. Patients and methods

2.1. Study design

This retrospective study reviewed consecutive patients with PNTM-associated CPA who were referred to the National Hospital Organization Kinki-chuo Chest Medical Center (KCMC) between January 1, 2010 and December 31, 2015. The patients' clinical data were collected from their medical records. CPA and PNTM were diagnosed using the European guideline on CPA [13] or the American Thoracic Society/Infectious Diseases Society of America criteria on PNTM [14], respectively. To this end, the following factors were examined: (1) clinical symptoms; (2) radiographic findings; (3) serological or biological evidence implicating *Aspergillus* species, including the *Aspergillus* precipitating antibody test (complement fixation test, BML) and the *Aspergillus* galactomannan antigen test (cut-off value: 0.5; enzyme-linked immunoassay, BML); (4) cultures of NTM and *Aspergillus* species from respiratory specimens. Simple aspergilloma, chronic cavitary pulmonary aspergillosis, and chronic fibrosing pulmonary aspergillosis were all included in the diagnosis of CPA [13]. This study was approved by the Institutional Review Board of KCMC (Approval number: 611).

We collected data regarding (1) the baseline characteristics of the patients; (2) underlying diseases; (3) corticosteroid use; (4) the date of CPA and PNTM diagnosis; (5) causative microorganisms; (6) sputum culture conversion; (7) radiographic findings; (8) serological findings at CPA diagnosis, including β-D glucan using the synthetic chromogenic substrate method (BML; cut-off value: 20 pg/mL); (9) treatment course; (10) outcome. NTM culture conversion was defined when there were three consecutive negative sputum cultures. Cases with one or two negative sputum culture results, but with no further sputum cultures available, were included in the culture conversion group. The radiographic features of NTM were classified on the basis of chest computed tomography (CT) according to the following patterns: nodular/bronchiectatic (NB) disease, fibrocavitary (FC) disease, and unclassifiable disease. CT findings with multiple nodules and bronchiectasis were defined as NB disease, and those with FC lesions were defined as FC disease [14]. None of the patients had any hypersensitivity-like disease or disseminated disease. If the radiographic abnormalities did not fit any specific pattern because of underlying pulmonary disease, we considered them as unclassifiable. Patients were followed through July 2017 or until death before July 2017. Survival status was obtained from the medical records.

2.2. Statistical analysis

Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test between patients with *Mycobacterium avium* complex (MAC) and those with *Mycobacterium kansasii*. A univariate assessment of selected risk factors was performed using the Cox proportional hazard model. To eliminate confounding factors from the prediction of mortality risk, variables with P-values < 0.05 in the univariate analysis were then entered into a multivariate assessment. The results are expressed as hazard ratios with corresponding 95% confidence intervals (CIs). All P-values < 0.05 were considered statistically significant. Data analyses were performed using JMP version 11.0 (SAS Institute Japan, Tokyo, Japan).

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3. Results

3.1. Baseline characteristics of study patients

Eighty-one patients were diagnosed with both CPA and PNTM during the study period. Of these, we excluded 19 whose CPA was diagnosed before their PNTM. Ultimately, the study population comprised 62 patients. The causative NTM species in the excluded patients were *M. avium* (eight patients), *M. intracellulare* (eight patients), *M. kansasii* (two patients), and *M. massiliense* (one patient).

The characteristics and underlying diseases of the patients with CPA and PNTM are detailed in Table 1. Their median age was 69.5 years, and 22 of the 24 women were never smokers. The major underlying diseases were chronic obstructive pulmonary disease (COPD), old pulmonary tuberculosis (TB), and interstitial lung disease (ILD). Only five patients (8%) had no comorbidities other than PNTM and CPA: three of the patients with MAC, and two of those with *M. kansasii*. Systemic corticosteroids were used in 16 patients, due to collagen disease, asthma, or cancer. The median dose of corticosteroids was 20 mg/day (range: 5–50 mg/day) and the median duration of corticosteroid therapy was 425 days (range: 31–2063 days). Biologics were not used in any patients.

3.2. Features of PNTM

MAC, including *M. avium* and *M. intracellulare,* was the most common cause of underlying PNTM, accounting for 60% of the all patients. *M. kansasii* was the second most common species, accounting for 32% of the patients. The remaining patients were diagnosed as having *M. szulgai*, *M. abscessus*, or *M. fortuitum*.

Upon imaging, the frequencies of NB disease and FC disease were the same, and 12 patients (20%) had a disease that was unclassifiable due to underlying pulmonary disease, mainly ILD. In some patients with NB disease, cavitary lesions were seen because of comorbidities such as COPD, old TB, and ILD.

Patients with MAC lung disease were mostly treated using a chemotherapy regimen that included clarithromycin (CAM), ethambutol (EB), and/or rifampin (RFP). Specifically, RFP/EB/CAM was used in 19 patients (51%), EB/CAM in six patients (16%), and RFP/CAM in two patients (5%). In refractory cases, streptomycin (SM), sitafloxacin (STFX), or levofloxacin (LVFX) were added. In cases of *M. kansasii*, isoniazid (INH), RFP, and EB were used in 70% of patients, and CAM and/or LVFX were added in some cases. In cases of *M. szulgai*, RFP, EB, CAM, INH, and LVFX were used. In cases of *M. fortuitum*, CAM, LVFX, and minocycline were included in the treatment regimen. In cases of *M. abscessus*, since infection control was difficult, amikacin, imipenem/cilastatin, CAM, RFP, STFX, and faropenem were used. Treatment drugs were discontinued in 22 patients, including eight who ceased taking RFP because azole antifungal therapy was introduced. Culture conversion of MAC and *M. kansasii* was observed in 18 (49%) and 17 (85%) patients respectively. All patients with *M. szulgai* and *M. abscessus* showed culture conversion. However, the patient with *M. fortuitum* continued to have positive culture sputum.

Table 1 – Patient characteristics (n=62).

Age, years		69.5	(42–87)
Sex, female/male		24/38	
Smoking, never/former or current		24/38	
Underlying disease			
	Old pulmonary tuberculosis	18	(29%)
	COPD	24	(39%)
	Diabetes mellitus	8	(13%)
	Interstitial lung disease	14	(23%)
	Asthma	7	(12%)
	Cancer	13	(21%)
	Collagen disease	11	(18%)
Use of systemic corticosteroids		16	(26%)
Mycobacterium species			
	Mycobacterium avium	23	(37%)
	Mycobacterium intracellulare	14	(23%)
	Mycobacterium kansasii	20	(32%)
	Mycobacterium szulgai	3	(4.8%)
	Mycobacterium abscessus	1	(1.6%)
	Mycobacterium fortuitum	1	(1.6%)
Radiologic features			
	NB	25	(40%)
	FC	25	(40%)
	Unclassifiable	12	(19%)
Cavitary lesion		43	(69%)
Treatment of PNTM, yes/no		52/10	
Treatment duration, days		440.5	(0–4187)
Time from diagnosis of PNTM to diagnosis of CPA, days		437	(0–7044)
Positive culture of *Aspergillus* species		55	(89%)
Positive *Aspergillus* antigen test		14	(23%)
Positive *Aspergillus* antibody test		25	(40%)
Treatment of *Aspergillus*, yes/no		42/20	
Treatment duration, days		36	(0–1800)
Hemosputum		33	(53%)
Surgical treatment		4	(6.5%)
Bronchial artery embolization		8	(13%)

Data are shown as medians (ranges) or Nos. (%).

COPD: chronic obstructive pulmonary disease, NB: nodular/bronchiectatic disease,

FC: fibrocavitary disease, PNTM: pulmonary non-tuberculous mycobacterial disease,

CPA: chronic pulmonary aspergillosis

3.3. Features of CPA

Among the patients with biologically confirmed CPA, the species of *Aspergillus* found in the respiratory specimens were *A. fumigatus* (41 patients), *A. niger* (seven patients), and *A. terreus* (one patient). In six cases, isolates of *Aspergillus* could not be identified at the species level. Antifungal therapy was initiated in 42 patients (68%). To treat CPA, itraconazole was used in 45% of patients, voriconazole in 26%, micafungin in

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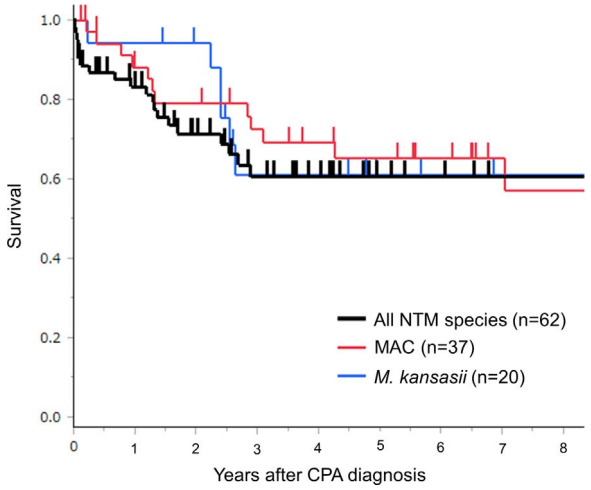

Fig. 1 – Survival curves of all-cause mortality from the diagnosis of CPA. Patients with all NTM species (black line, n = 62), MAC (red line, n = 37), and *M. kansasii* (blue line, n = 20). The 1- and 5-year survival rates of all patients were 83% and 61%, respectively. There was no significant difference between patients with MAC and those with *M. kansasii* (P = 0.938). CPA, chronic pulmonary aspergillosis; MAC, *Mycobacterium avium* complex; *M. kansasii*, *Mycobacterium kansasii*.

19%, and amphotericin B in 5%: medications overlapped in some cases.

Due to worsening hemoptysis, eight patients underwent bronchial artery embolization, and three had surgical lung resection for infection control.

3.4. *Mortality and risk factors*

The median follow-up period was 4.2 years (range: 0.1–14 years), and 22 patients died during the study period. The causes of death were: respiratory failure due to pulmonary infection (15 patients), hemoptysis (two patients), and COPD, lung cancer, cardiac failure, lung asbestosis, and unknown (one patient each). The causative organisms of pulmonary infection were methicillin-resistant *Staphylococcus aureus* (three patients), *Pseudomonas aeruginosa* (two patients), *Stenotrophomonas maltophilia* (two patients), and undetected (nine patients). Some patients displayed more than one infectious agent. The survival rate from the date of CPA diagnosis was 83% at 1 year and 61% at 5 years (Fig. 1). There was no significant difference in survival rate between MAC and *M. kansasii* (Fig. 1).

To determine the risk factors associated with mortality, we analyzed the data using Cox proportional hazard regression modelling. After univariate analysis, five significant risk factors for mortality were identified: use of systemic corticosteroids, non-NB disease (including FC disease and unclassifiable), cavitary lesions, non-use or discontinuation of RFP, and a C-reactive protein (CRP) level of ≥ 5.0 mg/dL at CPA diagnosis (Table 2). There was no significant correlation between mortality and (1) the causative NTM species, (2) the treatment regimen of NTM, (3) the culture conversion of NTM, and (4) the duration from NTM infection to CPA development. The significant risk factors identified by univariate analysis were then entered into multivariate analysis using a Cox proportional hazard regression model. The risk factors independently associated with overall mortality were use of systemic corticosteroids (hazard ratio [HR]: 3.32, 95% CI: 1.23–9.51; P = 0.0177) and CRP levels ≥ 5.0 mg/dL (HR: 8.96, 95% CI: 2.15–62.9; P = 0.0014) (Table 3).

4. Discussion

In the present study, we analyzed 62 patients with CPA and PNTM who were treated at our center. In previous reports, 3.9%–16.7% of patients with PNTM developed CPA [11,15,16], and 10%–46% of patients with CPA were infected with NTM [4,6,17], leading to increased mortality [10,12]. In the present study, we focused on the correlations between CPA and PNTM and investigated the prognosis and mortality risk of CPA in patients with PNTM.

Table 2 – Univariate analysis of risk factors for overall mortality among patients with PNTM and CPA.

	Hazard ratio (95% CI)	P-value
Male sex	1.05 (0.443–2.66)	0.910
Age ≥ 70 years	1.71 (0.703–4.26)	0.235
Current or former smoker	1.39 (0.579–3.69)	0.466
Use of systemic corticosteroids	6.60 (2.74–16.8)	< 0.0001*
Non-NB disease	2.60 (1.01–8.01)	0.0481*
Cavitary lesion	4.95 (1.43–31.1)	0.0086*
No NTM culture conversion	1.51 (0.615–3.59)	0.356
Non-use or discontinuation of RFP	3.73 (1.44–11.5)	0.0061*
Time from diagnosis of PNTM to CPA (> 1 year)	0.532 (0.211–1.26)	0.154
β-D-glucan ≥ 20 pg/mL	1.81 (0.732–4.69)	0.198
Aspergillus antigen positive	2.63 (0.947–6.91)	0.0627
CRP ≥ 5 mg/dL at diagnosis of CPA	19.4 (5.44–124)	< 0.0001*
Hb < 12 g/dL at diagnosis of CPA	2.36 (0.975–5.88)	0.0569
Hemoptysis	0.571 (0.238–1.46)	0.238

RFP: rifampin, CPA: chronic pulmonary aspergillosis, CRP: C-reactive protein, Hb: hemoglobin.
* P<0.05. PNTM: pulmonary nontuberculous mycobacterial disease, NB: nodular bronchiectatic.

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Table 3 – Multivariate analysis of risk factors for overall mortality among patients with PNTM and CPA.

	Hazard ratio (95% CI)	P-value
Use of systemic corticosteroids	3.32 (1.23–9.51)	0.0177*
Non-NB disease	1.31 (0.409–5.74)	0.664
Cavitary lesion	1.97 (0.293–16.6)	0.484
Non-use or discontinuation of RFP	1.40 (0.482–4.65)	0.547
CRP ≥ 5 mg/dL at diagnosis of CPA	8.96 (2.15–62.9)	0.0014*

RFP: rifampin, CPA: chronic pulmonary aspergillosis, CRP: C-reactive protein.
* $P<0.05$. PNTM: pulmonary nontuberculous mycobacterial disease, NB: nodular bronchiectatic.

We found that, in patients with PNTM-associated CPA, poor outcomes were associated with use of systemic corticosteroids and high CRP levels at CPA diagnosis. Underlying disease other than PNTM, hemoptysis, species and treatment of NTM, and disease duration from NTM infection to CPA development were not significantly correlated with overall mortality. Use of corticosteroids has been reported as an independent risk factor for CPA in patients with PNTM [18], and the present research suggests that it is a poor prognostic factor among patients with both CPA and PNTM. Furthermore, Nakamoto et al. reported that baseline corticosteroid use, CRP level ≥ 5.0 mg/dL, older age, systemic comorbidities, and body mass index (BMI) < 18.5 kg/m^2 were negative prognostic factors for all-cause chronic necrotizing pulmonary aspergillosis mortality [17]. Conversely, non-NB disease, low BMI, and anemia have been reported as poor prognostic factors for MAC lung disease, which is the most common type of PNTM [19]. It follows that the negative prognostic factors of CPA in patients with PNTM are closely related to the risk factors for CPA rather than for PNTM.

The 1- and 5-year survival rates from CPA diagnosis in the present study were 83% and 61%, respectively. These results were similar to those of studies from England (n = 387; 86%, 62%, and 47% at 1, 5, and 10 years, respectively [10]) and Japan (n = 194; 49% and 34% at 5 and 10 years, respectively [17]). Takeda et al. reported that all-cause mortality in the NTM plus CPA co-infection group was similar to that in the CPA group, indicating that NTM does not affect CPA outcomes [18]. It may be that the population of the present study differed from those of other studies. However, the survival rate in patients with PNTM-associated CPA was fairly close to that in all CPA patients.

In Japan, the species implicated in PNTM are MAC (83%), *M. kansasii* (8%), and rare species (9%) [20]. We investigated all PNTM patients referred to our institution during the study period and found that the frequency of MAC was lower, while that of *M. kansasii* was slightly higher, than the previous Japanese report: MAC occurred in 62% to 73% of patients, *M. kansasii* in 9% to 15%, and other species in 17% to 23%. Importantly, there was no major construction or destruction of buildings around the hospital area during the study period. In patients who developed CPA, the NTM species were MAC (60%), *M. kansasii* (32%), and other species (8%). A high proportion of patients infected with *M. kansasii* also developed CPA, considering the distribution of NTM species in Japan and our institution. For comparison, in patients who did not develop CPA, the NTM species were MAC (68%), *M. kansasii* (11%), and other species (21%). Fujiuchi et al. reported that, since *M. kansasii* infection tends to cause cavity lesions, it was more likely than other *Mycobacterium* species to be complicated by CPA [16]. Griffith et al. reported that, in patients with *M. kansasii*, chest radiographic changes were similar to those seen after reactivation of pulmonary TB, including cavitary infiltrates with an upper lobe predilection. In some case series, approximately 90% of patients with *M. kansasii* disease had cavitary infiltrates [21]. The present report suggests that underlying diseases that cause cavity lesions, especially *M. kansasii* infection, might be an important risk factor for CPA.

RFP is a key drug for the treatment of *M. kansasii*, and it is also used to treat MAC. Discontinuation of RFP due to drug interaction with azoles such as voriconazole and itraconazole, which are used to treat CPA, is controversial in the case of patients with both CPA and PNTM. However, in the present research, treatment with RFP did not influence survival. Since the clinical course of CPA seems to have a stronger effect on prognosis, it seems that the discontinuation of RFP has no major impact on the treatment of patients with CPA and PNTM.

There were some limitations in this study. As it was a retrospective study, some clinical and laboratory records were not available. In addition, the underlying pulmonary diseases made it difficult to distinguish the radiological findings of PNTM and CPA. All patients showed positive culture for *Aspergillus* species from respiratory samples, or were positive for *Aspergillus* antigen and/or antibody, and all displayed clinical and radiological features. However, some might have been colonized patients. Lastly, we studied only a small number of patients at a single institution, and there was no control group; to obtain more information about CPA in patients with PNTM, large-scale studies are needed.

5. Conclusions

CPA is more likely to develop in patients with PNTM who have MAC and *M. kansasii* infections than in those infected with other species of NTM. The use of systemic corticosteroids and high CRP levels at CPA diagnosis were associated with high mortality risk. Since the outcomes of CPA are poor, clinicians should be aware of this disease when managing PNTM, especially in patients with other underlying diseases. Early diagnosis and referral, as well as improved treatments, are required.

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None.

Conflict of interest

The authors have no conflicts of interest to declare.

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REFERENCES

[1] Field SK, Cowie RL. Lung disease due to the more common nontuberculous mycobacteria. Chest 2006;129:1653–72.
[2] Glassroth J. Pulmonary disease due to nontuberculous mycobacteria. Chest 2008;133:243–51.
[3] Winthrop KL, McNelley E, Kendall B, Marshall-Olson A, Morris C, Cassidy M, et al. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. Am J Respir Crit Care Med 2010;182:977–82.
[4] Jhun BW, Jeon K, Eom JS, Lee JH, Suh GY, Kwon OJ, et al. Clinical characteristics and treatment outcomes of chronic pulmonary aspergillosis. Med Mycol 2013;51:811–7.
[5] Lee J-K, Lee YJ, Park SS, Park JS, Cho Y-J, Park YS, et al. Clinical course and prognostic factors of pulmonary aspergilloma. Respirology 2014;19:1066–72.
[6] Ohba H, Miwa S, Shirai M, Kanai M, Eifuku T, Suda T, et al. Clinical characteristics and prognosis of chronic pulmonary aspergillosis. Respir Med 2012;106:724–9.
[7] Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J 2011;37:865–72.
[8] Kunst H, Wickremasinghe M, Wells A, Wilson R. Nontuberculous mycobacterial disease and Aspergillus-related lung disease in bronchiectasis. Eur Respir J 2006;28:352–7.
[9] Committee for Guideline for Management of Deep-seated Mycoses. Guidelines for management of deep-seated mycoses 2014. Tokyo, Japan: Kyowa Kikaku Ltd.; 2014. Japanese.
[10] Lowes D, Al-Shair K, Newton PJ, Morris J, Harris C, Rautemaa-Richardson R, et al. Predictors of mortality in chronic pulmonary aspergillosis. Eur Respir J 2017:49.
[11] Zoumot Z, Boutou AK, Gill SS, van Zeller M, Hansell DM, Wells AU, et al. Mycobacterium avium complex infection in non-cystic fibrosis bronchiectasis. Respirology 2014;19:714–22.
[12] Jhun BW, Jung WJ, Hwang NY, Park HY, Jeon K, Kang ES, et al. Risk factors for the development of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease. PLoS One 2017;12:e0188716.
[13] Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J 2016;47:45–68.
[14] Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respr Crit Care Med 2007;175:367–416.
[15] Ishikawa S, Yano S, Kadowaki T, Wakabayashi K, Kimura M, Kobayashi K, et al. Clinical analysis of non-tuberculous mycobacteriosis cases complicated with pulmonary aspergillosis. Kekkaku 2011;86:781–5. Japanese.
[16] Fujiuchi S, Sakunami M, Yamamoto Y, Takeda A, Nishigaki Y, Fujita Y, et al. Analysis of chronic necrotizing pulmonary aspergillosis (CNPA) cases complicated with non-tuberculous mycobacteriosis (NTM). Kekkaku 2008;83:573–5. Japanese.
[17] Nakamoto K, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Prognostic factors in 194 patients with chronic necrotizing pulmonary aspergillosis. Intern Med 2013;52:727–34.
[18] Takeda K, Imamura Y, Takazono T, Yoshida M, Ide S, Hirano K, et al. The risk factors for developing of chronic pulmonary aspergillosis in nontuberculous mycobacteria patients and clinical characteristics and outcomes in chronic pulmonary aspergillosis patients coinfected with nontuberculous mycobacteria. Med Mycol 2016;54:120–7.
[19] Hayashi M, Takayanagi N, Kanauchi T, Miyahara Y, Yanagisawa T, Sugita Y. Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2012;185:575–83.
[20] Sakatani M. The non-tuberculous mycobacteriosis. Kekkaku 2005;80:25–30. Japanese.
[21] Griffith DE. Management of disease due to Mycobacterium kansasii. Clin Chest Med 2002;23:613–21.

Please cite this article as: Naito M, et al. Prognosis of chronic pulmonary aspergillosis in patients with pulmonary non-tuberculous mycobacterial disease. Respiratory Investigation (2018), https://doi.org/10.1016/j.resinv.2018.04.002