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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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