A pilot study for Basidiomycete-associated chronic cough: A potential contributor to refractory and unexplained or refractory chronic cough

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Article

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Abstract

Recent evidence suggests a potential association between chronic cough and environmental fungi, particularly basidiomycetes, giving rise to the concept of fungus-associated chronic cough (FACC). However, the role of basidiomycetes in chronic cough remains poorly understood. In this pilot study, we investigated 30 patients with unexplained or refractory chronic cough (UCC/RCC) and 30 patients with other respiratory diseases (non-chronic cough). Spontaneous sputum samples were collected for fungal culture, and participants completed a cough and sputum symptom questionnaire, underwent chest computed tomography, and were evaluated for underlying diseases and medication use. Analyses were conducted by chronic cough status and by basidiomycete detection. Basidiomycetes were detected in the sputum of 9 out of 30 chronic cough patients but in none of the non-chronic cough patients (P = 0.0019), with a significant seasonal peak from June to August (P = 0.0419). No associations were observed with age, sex, underlying diseases, cough severity, or high-resolution computed tomography findings. These results indicate that basidiomycete colonization may contribute to FACC in individuals with UCC/RCC, particularly during the summer months.

Introduction

Coughing is a biological defense response to expel foreign substances and secretions from the airways. Chronic cough is defined as a cough that persists for 8 weeks or longer. [1] [2] In Japan, asthma-related cough is the most common cause of chronic cough; other common causes include atopic cough, gastroesophageal reflux disease, sino-bronchial syndrome, and post-infectious cough. [3] [4] [5] Unexplained chronic cough (UCC) or refractory chronic cough (RCC) may also occur even with appropriate treatment of the underlying disease. Although several drug therapies, such as pregabalin [6] and P2X3 receptor antagonists, [7] have shown efficacy, an appropriate treatment algorithm for UCC/RCC has not been sufficiently validated.

In 2009, Ogawa et al. reported a new disease called “fungus-associated chronic cough” (FACC). [8] FACC is defined as chronic cough in patients from whom environmental fungi are cultured in sputum and treated with a low dose of itraconazole. Basidiomycetes such as *Bjerkandera adusta* are considered the most important environmental fungi in the FACC. Despite conventional cough treatments, FACC does not improve, and patients with UCC/RCC may include those with FACC. [9] However, these studies were limited to a single institution. The accurate detection of basidiomycetes in clinical specimens is challenging and there is no consensus on the laboratory method for their detection in airway samples. Consequently, the exact prevalence remains unknown.

In addition, basidiomycetes are detected year-round in outdoor or indoor environments but are more frequently detected in summer. [10] [11] [12] It has also been reported that the abundance of basidiomycetes is affected not only by temperature but also by humidity, [13] [14] and there is a possibility that the onset of FACC is also seasonal. Ogawa et al. subsequently reported additional cases suggestive of FACC; [15] [16] however, the number of such cases was insufficient, and the sensitivity and specificity of the isolation and culture methods for basidiomycetes remain unknown. Therefore, it cannot be definitively stated that basidiomycetes in the airways cause chronic coughing or its subsequent pathogenesis.

In the present pilot study, we aimed to investigate the reproducibility of findings related to FACC in a region different from that previously reported. Specifically, we performed fungal cultures of sputum from patients with UCC/RCC to determine whether basidiomycetes could be isolated in Nagasaki. Additionally, we compared the background factors of patients with chronic cough in whom basidiomycetes were detected.

Results

Participant Characteristics

Sixty patients participated in the study and were divided into two groups: the CC group (n = 30) and the NC group (n = 30). Sputum samples were collected through self-expectoration from all participants. Table 1 summarizes the clinical characteristics of the study participants. Age did not differ significantly between the two groups (68.0 (10.2) years vs. 66.2 (12.9) years). In the CC group, there were seven males and 23 females, while the NC group had 14 males and 16 females (P = 1.000). Smoking history was present in 11 patients in the CC group and 20 in the NC group (P = 0.201).

In the CC group, underlying diseases included bronchial asthma (22 patients), COPD (3), sinusitis (including sinus bronchial syndrome; 8), gastroesophageal reflux disease (2), and a history of thyroid tumor surgery (3). Two patients had UCC, and 28 patients had RCC that did not respond to treatment.

In the NC group, 29 patients had lung tumors (16 adenocarcinomas, 6 small-cell carcinomas, 2 thymomas, 1 malignant scleral mesothelioma, 1 pulmonary artery vascular sarcoma, and 3 unknown histology). Among them, six had interstitial lung disease and five had COPD. One case of radiation pneumonitis was observed; however, there were no cases of bronchial asthma.

In the CC group, 22 patients received regular inhaled steroids, 11 received macrolide antibacterial agents, and 2 received amphotericin B oral solution. In the NC group, one patient received tetracyclines.

Fungal culture results showed that basidiomycetes were detected in 9 of CC group, whereas none were detected in NC group (P = 0.0019).

Identification of Basidiomycetes in Sputum Cultures

Genetic analysis showed that the genera such as *Irpex* (*Irpex laceratus* and *Emmia lacerata*) were detected in five cases; *Phanerochaete* in three; *Phanerodontia* and *Trametes* in two; *Bjerkandera*, *Ceriporia*, *Crepatura*, *Perenniporia*, *Phlebia*, and *Rigidoporus* in one (Table 2). In addition to basidiomycetes, *Penicillium* were detected in four cases, each of *Phomopsis* and *Crepatura ellipsospora* were detected in one case (Supplement).

Monthly Number of Sputum Collection and Basidiomycetes Positivity and Monthly Humidity Average in Nagasaki City

Figure 1 illustrates the monthly number of sputum collections, Basidiomycetes positivity, and average monthly humidity and temperature in Nagasaki. Basidiomycetes were not detected in sputum collected during the winter months from November to February. The monthly humidity average in Nagasaki correlated with the monthly detection rate of basidiomycetes in CC group (P = 0.0039, R^2 = 0.58; Fig. 2A). Similarly, the average monthly temperature was also correlated with the monthly detection rate of basidiomycetes in the CC group (P = 0.0073, R2 = 0.53; Fig. 2B).

Background Comparison of Patients with Chronic Cough: Sputum Basidiomycetes Detected vs. Not Detected

Table 3 compares the background characteristics of patients with chronic cough with and without basidiomycetes detected in sputum. Among patients with chronic cough, there were no significant differences in age, sex, smoking history, use of antibacterial and antifungal agents, inhaled steroids, proton pump inhibitor or comorbidities

(bronchial asthma, COPD, sinusitis, or reflux esophagitis) between the patients detected and not detected basidiomycetes. No significant differences were seen in VAS and CAT scores. High-resolution computed tomography (HRCT) of the lungs at the time of sputum collection revealed cavitary lesions, bronchiectasis, and mucus plugs in some cases; however, no significant differences were seen between the two groups. About the timing of specimen collection, basidiomycetes were significantly more frequently detected in specimens collected between June and August (P = 0.0419). Of the nine cases basidiomycetes were detected in, two or more species were detected in four cases, but the background factors mentioned above did not differ from the other five cases (data not shown).

Discussion

The primary results of this study were as follows: basidiomycetes were detected in the sputum of 9 of 30 patients with chronic cough, while no basidiomycetes were found in 30 patients with non-chronic cough (P = 0.0019). Additionally, basidiomycetes were detected only in sputum samples collected between June and August (P = 0.0419).

Our study, conducted in a different region than previously reported, found no basidiomycetes in patients with non-chronic cough. Thirty percent of the patients with chronic cough had basidiomycetes in their sputum. Previous reports have implicated basidiomycetes, including *B. adusta*, in airway colonization in patients with airway lesions, such as bronchial asthma, COPD, chronic sinusitis, and interstitial pneumonia. [17] [18] [19] [20] In our study, basidiomycetes were detected in five patients with bronchial asthma, three with chronic sinusitis, and one with COPD, suggesting that some patients with chronic cough may have basidiomycete colonization and be diagnosed with RCC. Although there were no significant differences in use of inhaled steroids between the patients detected and not detected basidiomycetes, it is necessary to increase the sample size and continue the study. A previous report found *B. adusta* in 14 of 31 patients with fungal allergic bronchopulmonary aspergillosis (FACC), and other basidiomycetes in 17 patients. [21] However, reports on the types and frequencies of other basidiomycete species are scarce. In our study, we detected 10 genera of the phylum Basidiomycota, with *Irpex* being the most frequently isolated and *Bjerkandera* detected in only one case. Although *Bjerkandera* is reported to be more frequently detected outdoors compared with *Cladosporium*, *Penicillium*, *Alternaria*, and *Aspergillus*, [22] the species isolated from different regions may vary.

Basidiomycetes, such as *B. adusta*, have been implicated as causative antigens in allergic bronchopulmonary mycosis. [23] Fifteen percent of patients with chronic cough with detected basidiomycetes had mucus plugs in the bronchioles based on HRCT findings. [24] In our study, mucous plugs were found in the peripheral airways of two of nine patients (22.2%) with detected basidiomycetes. Previous reports suggested allergic cough due to basidiomycetes sensitization based on increased eosinophils in sputum of patients with FACC and the results of bronchial provocation and lymphocyte stimulation tests using *B. adusta* antigen solution. [25] However, in our study, we used self-expectorated sputum rather than induced sputum for culture testing, and we did not use the Miller & Jones or Geckler classifications, so the quality of the sputum samples varied, and the basidiomycetes detected may have been established in the upper respiratory tract, including the pharyngeal mucosa. Our study did not evaluate eosinophils in sputum, and no report has definitively verified this association. Further interventional studies are needed to elucidate the pathogenesis of chronic cough in patients with basidiomycosis, including antifungal agent administration and reexamination of sputum cultures after symptom improvement.

B. adusta is widely distributed indoors and outdoors globally but is mainly detected in summer. [10] In the present study, no basidiomycetes were detected in samples collected during winter. Additionally, humidity correlated with the detection rate of basidiomycetes. Our results may suggest that basidiomycetes cause chronic coughing, especially during summer. In our study, no antifungal drugs were administered to patients with basidiomycosis, and there was no seasonal variation in cough symptoms in cases where basidiomycosis was detected. As there have been no previous reports of seasonal variation in cough symptoms in patients diagnosed with FACC, it is necessary to conduct follow-up surveys of patients where basidiomycosis was detected. Since basidiomycetes are rarely detected in microbiological sputum examinations in general medical facilities, cases of FACC may be overlooked. In patients with chronic cough unresponsive to appropriate treatment, sputum culture using fungal medium should be considered with FACC in mind. The limitations of this pilot study included the small sample size, timing of specimen collection, and bias in comorbidities. Additionally, a causal relationship between basidiomycetes isolation and symptoms has not been proven. Large-scale observational studies and interventional trials are needed to evaluate symptom improvement following antifungal treatment.

Conclusion

In Nagasaki, a region distinct from those previously reported, basidiomycetes were detected in the sputum of 30% of patients with chronic cough, while they were entirely absent in patients without chronic cough. The correlation between season and humidity with the frequency of basidiomycete identification indirectly underscores the clinical significance of fungal airway colonization and contamination.

Methods

Study Design

Between June 1, 2022, and March 31, 2024, patients with UCC/RCC who live in Nagasaki City and visited our respiratory medicine outpatient clinic or were admitted to the respiratory medicine department at our institution were included in the chronic cough group (CC group). Spontaneous sputum samples were collected from these patients after obtaining their consent. Additionally, patients admitted to our department for the examination or treatment of respiratory diseases (such as lung cancer or interstitial pneumonia) were included in the non-chronic cough group (NC group). These patients had no cough symptoms or obvious airway infections and were able to provide sputum samples. Patients with a performance status of 3 or higher, poor general condition, or difficulty in self-expectorating were excluded from the study. The collected sputum samples were subjected to fungal cultures on the same day. This single-center, prospective, observational study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of our institution (Approval No. 23091101).

Diagnosis of Chronic Cough

According to the 2019 guidelines of the Japanese Respiratory Society for the treatment of cough and sputum, patients with persistent cough symptoms lasting for more than 8 weeks are diagnosed with chronic cough. [1] UCC refers to chronic coughing of unknown origin that persists despite adequate treatment, including empiric therapy. chronic cough that does not improve even with appropriate treatment for conditions such as cough asthma and gastroesophageal reflux disease is referred to as RCC. [26]

Mycological Study

Sputum samples collected from the patients were applied to Sabouraud dextrose agar (210950, Becton, Dickinson and Company, BD, Tokyo, Japan) and incubated at 30 °C for 2 weeks. Emergent basidiomycete colonies were isolated on potato dextrose agar (213400, BD Biosciences) and cultured in pure form. Additionally, some colonies were cultured on potato dextrose agar slant medium at 30 °C for 1 week. DNA was extracted from the fungal isolates and amplified by PCR using primers 18SF1 (5´-AGGTTTCCGTAGGGTGAACCT-3´) and 58SR1 (5´-TTCGCTGCGTTCTTCATCGA-3´). Specific primers BjF3 (5´-ACCTTGCGCTCCTTGGTAT-3´) for *B. adusta*, a basidiomycete, and BjR3 (5´-CTCCACAGCAACGCAGAT-3´) were designed. Using the Polymerase-Chain-Reaction (PCR) products, other fungal species were identified using the Basic Local Alignment Search Tool (BLAST) database (https://macrogen-japan.co.jp/service/sequencing/).

Evaluation of Cough and Sputum Symptoms

The visual analog scale (VAS) for cough severity is a 100 mm straight line scale that patients use to assess the severity of their cough, from “no cough symptoms” (0 mm) to “the worst cough imaginable” (100 mm). [27] The chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) is a validated self-report measure for assessing COPD symptoms. It is comprised of eight questions related to cough and sputum symptoms. Specifically, we used the scores from questions 1 (cough symptoms) and 2 (sputum symptoms). The scoring system ranged from 0 to 5, with higher scores indicating more severe symptoms. [28]

Measurement of average monthly humidity in Nagasaki City

The monthly average humidity for Nagasaki City was obtained from data observed by the Japan Weather Association using a hygrometer (https://www.jma.go.jp/jma/index.html).

Statistical Analyses

Statistical analyses were performed using the JMP® Pro software version 16.0.0 (SAS Institute, Cary NC). Continuous variables were presented as mean (standard deviation; SD). Differences between groups were assessed using the Wilcoxon’s rank sum test or Fisher’s exact probability test. Additionally, we investigated the correlation between the monthly mean humidity in Nagasaki and the detection rate of basidiomycetes in sputum using linear regression analysis. Statistical significance was set at a $P < 0.05$.

Declarations

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Data availability

The datasets analyzed during the current study available from the corresponding author on reasonable request.

Declaration of Competing Interest

There are no conflicts of interest to declare.

Author Contributions Statement

JI, SF, CFand YO conceived and designed the study. JI, SF, CF, and YO contributed to sample collection and interpretation. TT, ST, NS,and TN assisted in data analysis and interpretation of results. HM provided critical revision of the manuscript. JI drafted the manuscript. All authors reviewed, edited, and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in compliance with all applicable laws and regulations concerning the protection of participants' privacy. Ethical approval was obtained from the Nagasaki University Hospital Clinical Research Ethics Committee in accordance with the "Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects" (Approval No.: 23091101-3). Written informed consent was obtained from all participants prior to study enrollment.

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Tables

Table 1. Clinical characteristics of the CC and NC groups

	CC group, n=30	NC group, n=30	P value
Age, mean	68.0	66.2	0.5587
Female, n (%)	23 (76.7)	16 (53.3)	0.1033
Smoking status			
Never smoker, n (%)	19 (63.3)	10 (33.3)	0.0201
Current or former smoker, n (%)	11 (36.7)	20 (66.7)	
Medications			
Inhaled corticosteroids, n (%)	22 (73.3)	0 (0)	<0.0001
Antibacterial drug, n (%)	14 (46.7)	1 (0.3)	0.0004
Antifungal agent, n (%)	2 (6.67)	0 (0)	0.4915
Detection of Basidiomycete, n (%)	9 (30.0)	0 (0.0)	**0.0019**

CC, chronic cough; NC, non chronic cough.

Table 2. Identified basidiomycetes

Basidiomycete species	N
Irpex	5
Phanerochaete	3
Phanerodontia	2
Trametes	2
Bjerkandera	1
Ceriporia	1
Perenniporia	1
Rigidoporus	1
Crepatura	1
Phlebia	1

Table 3. Background comparison of patients with chronic cough between those with and without detected basidiomycetes

Variables	With Basidiomycete (n = 9)	Without Basidiomycete (n = 21)	P values
Age, years, mean	69.7	64.8	0.2295
Female, n (%)	7 (77.78)	16 (76.2)	1.0000
Smoking status	-	-	
Never smoker, n (%)	7 (77.8)	12 (57.1)	0.4189
Current or former smoker, n (%)	2 (22.2)	0 (0)	
Medications			
Antibacterial drug, n (%)	3 (33.3)	10 (47.6)	0.6908
Antifungal agent, n (%)	0 (0)	2 (9.5)	1.0000
Proton pump inhibitor, n (%)	4 (44.4)	8 (38.1)	1.0000
Inhaled corticosteroid, n (%)	6 (66.7)	16 (76.2)	0.6662
VAS, mean	45.0	51.1 (31.6)	0.6446
COPD assessment test			
Q1 (frequency of coughing), mean	2.6	2.6	0.6240
Q2 (Frequency of sputum), mean	3.0	3.1	0.3609
Q1+Q2, mean	5.6	4.9	0.9441
Underlying disease			
UCC, n (%)	1 (11.1)	1 (4.8)	0.5172
RCC, n (%)	8 (88.9)	20 (95.2)	
Bronchial asthma, n (%)	5 (55.6)	17 (81.0)	0.1954
COPD, n (%)	1 (11.1)	2 (9.5)	1.0000
Chronic rhinosinusitis, n (%)	3 (33.3)	5 (23.8)	0.6662
Gastroesophageal reflux, n (%)	0 (0)	2 (9.5)	1.0000
Sample collection timing			
June-August, n (%)	6 (66.7)	5 (23.8)	**0.0419**
September-May, n (%)	3 (33.3)	16 (76.2)	
HRCT findings			
Cavity, yes, n (%)	2 (22.2)	2 (9.5)	0.5632
Bronchiectasis, yes, n (%)	2 (22.2)	5 (23.8)	1.0000
Mucoid impaction, yes, n (%)	2 (22.2)	5 (23.8)	1.0000

VAS, the visual analog scale; COPD, chronic obstructive pulmonary disease; UCC, Unexplained chronic cough; RCC, Refractory chronic cough; HRCT, high-resolution computed tomography.

Figures

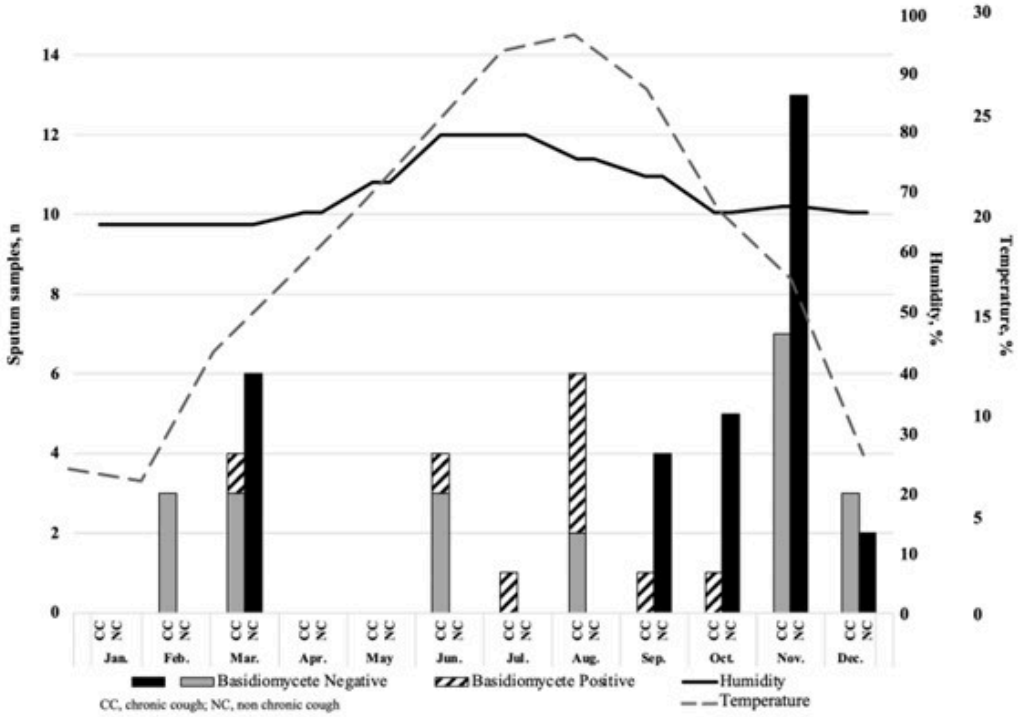

Figure 1

Basidiomycetes were not detected in sputum collected during the winter months from November to February.

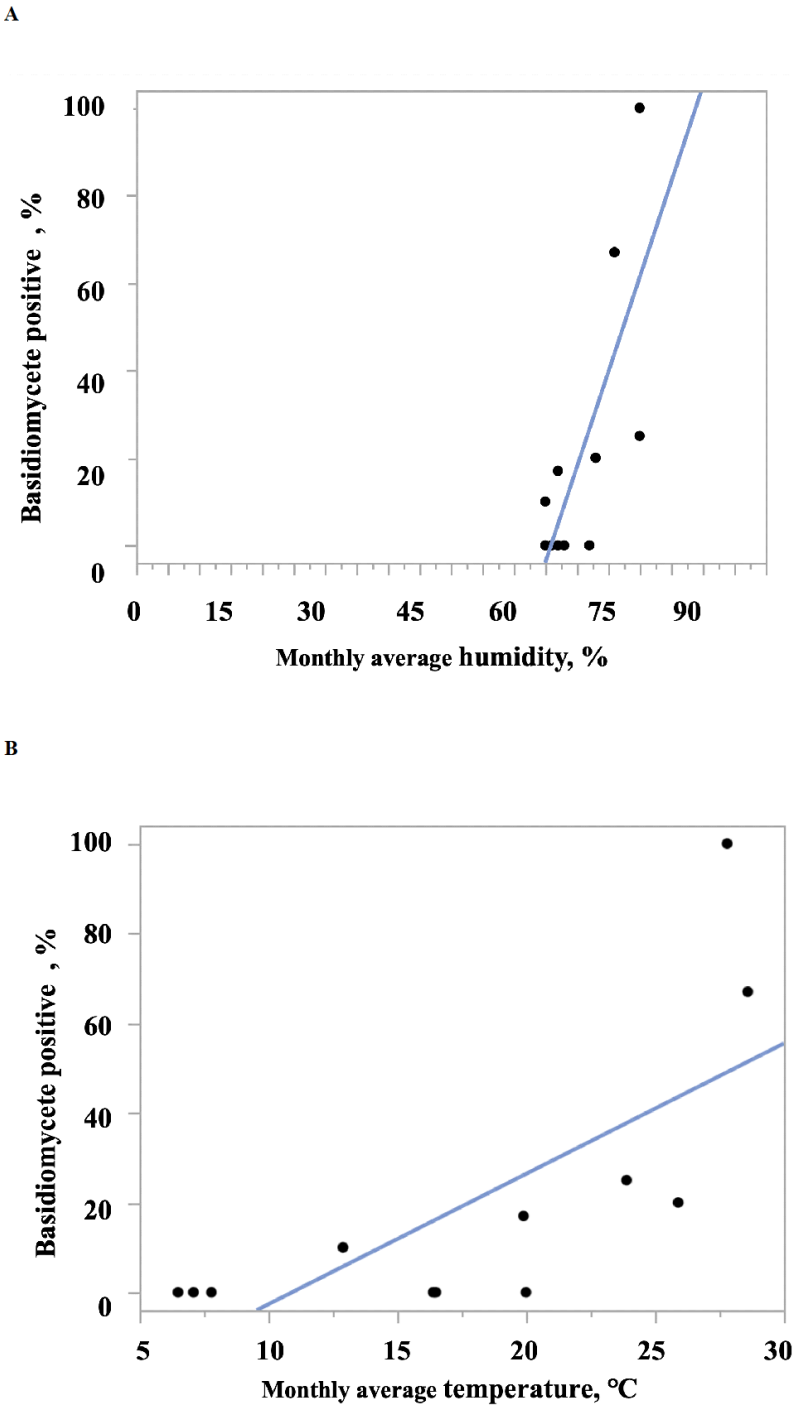

Figure 2

The monthly humidity average in Nagasaki correlated with the monthly detection rate of basidiomycetes in CC group ($P = 0.0039$, $R^2 = 0.58$).