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CASE REPORT

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Exophiala dermatitidis coinfection with nontuberculous mycobacteria: A case report and literature review

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Abstract

Six years ago, a 60-year-old man presented to our hospital with a cough and sputum. Upon suspicion of nontuberculous mycobacterial (NTM) infection, he was followed up at our hospital. Because the abnormal shadows in the bilateral lung fields deteriorated slightly over 6 years, bronchoscopy was performed. *Exophiala dermatitidis* and *Mycobacterium intracellulare* were detected in the bronchial lavage fluid. The patient underwent follow-up examinations without drug administration. Currently, the patient's condition remains stable. *E. dermatitidis* is regulatory found in the lungs of patients with cystic fibrosis, but only rarely is it found in respiratory samples from patients without cystic fibrosis. However, NTM complications have been reported more frequently in recent years. Due to the increasing number of NTM patients, *E. dermatitidis* pulmonary infections may also increase. Additional research is required to develop strategies for treating this infection.

KEYWORDS

bronchiectasis, *Exophiala dermatitidis*, nontuberculous mycobacteria

INTRODUCTION

Exophiala dermatitidis is a black fungus that is distributed worldwide in natural environments, such as soil and dead plant material. This fungus is regularly isolated from respiratory samples of cystic fibrosis (CF) patients as colonies and sometimes causes exacerbations.[1–3] Pulmonary infections caused by *E. dermatitidis* have been reported in non-CF patients, albeit rarely compared to CF patients.[4–18]

Here, we describe a case of *E. dermatitidis* coinfection with nontuberculous mycobacteria (NTM) and review clinical reports describing the features of pulmonary infections caused by *E. dermatitidis* in non-CF patients.

CASE REPORT

Six years ago, a 60-year-old man presented to our hospital with a cough and sputum. Chest computed tomography revealed nodules, infiltrative shadows, and bronchiectasis in the right middle and left upper lobes (Figure 1A). Upon suspicion of NTM infection, the patient was followed up at our hospital. He had no history of smoking or allergies. He had been diagnosed with prostatitis, but there were no past histories of respiratory diseases. Laboratory data showed a white blood cell count of 3860/μL and C-reactive protein level of 0.05 mg/dL. Tests for β-D-glucan, anti-aspergillus antigen, and anti-cryptococcus antigen returned negative results but that for anti-*Mycobacterium avium* complex antibody returned positive results. His symptoms improved by the administration of expectorant 3 months later of first visit. But after 6 years, the abnormal shadows in the bilateral lung fields deteriorated slightly (Figure 1B). Therefore, bronchoscopy was performed. Filamentous fungi (Figure 1C) and *Mycobacterium intracellulare* were detected in the bronchial lavage fluid. After 25 days of culturing the fungi at 35°C, olive-black colonies grew on a potato-dextrose agar (Figure 1D). Sequencing analysis of the internal transcribed

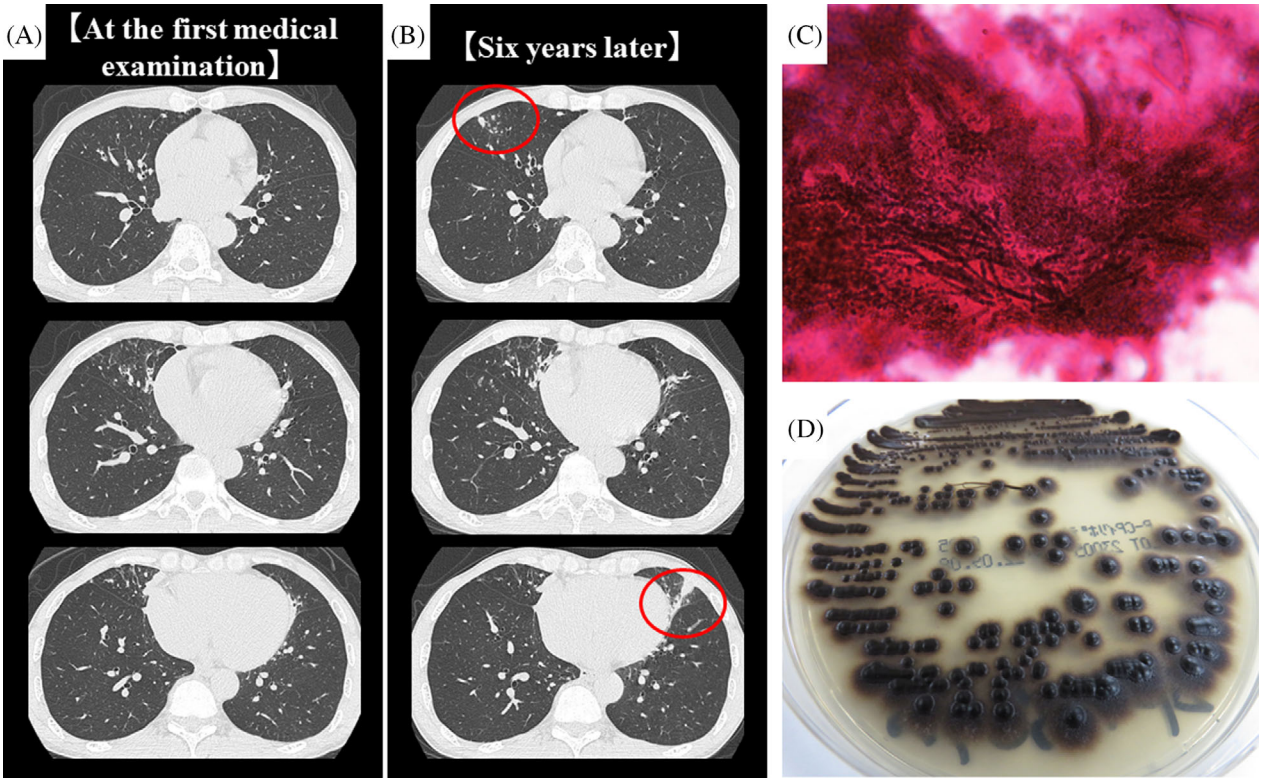

FIGURE 1 Chest computed tomography (CT) findings (A, B). (A) CT at the first medical examination showed nodules, infiltrative shadows, and bronchiectasis in the right middle and left upper lobes. (B) Six years later, these shadows were partially deteriorated (red circle). Microscopic and Macroscopic findings of the fungi from the bronchial lavage fluid (C, D). (C) Gram staining of bronchial lavage fluid showed filamentous fungi (×1000). (D) Olive-black colour colonies were detected after culturing the fungi for 25 days in potato-dextrose agar incubated at 35°C.

TABLE 1 Summary of non-cystic fibrosis patients with pulmonary *Exophiala dermatitidis* infection.

Author (references)	Age	Sex	Region	Underlying disease	Symptoms	Treatment	Outcome
Barenfanger et al.[4]	79	F	USA	Bronchiectasis	Hemoptysis, fever	AMPH-B, 5-FC	Survival
Kenney et al.[5]	21	F	USA	Chronic granulomatous disease	Fever, chill, shortness of breath	Op, AMPH-B, 5-FC, FLCZ	Survival
Mukaino et al.[6]	54	F	Japan	Bronchiectasis	Cough, sputum	MCZ, AMPH-B	Survival
Taj-Aldeen et al.[7]	54	F	Qatar	Diabetes, cervical cancer	Cough, sputum, hemoptysis	FLCZ, ITCZ, AMPH-B	Death
Ozawa et al.[8]	81	F	Japan	None	Hemoptysis	ITCZ	Survival
Tanamachi et al.[9]	53	F	Japan	Bronchiectasis	Sputum, chest pain	MCZ, 5-FC, ITCZ	Survival
Bulloch[10]	86	F	USA	Dementia	No symptoms	VRCZ	Survival
Suzuki et al.[11]	65	M	Japan	Multiple myeloma	No symptoms	VRCZ, Op	Survival
Mukai et al.[12]	63	F	Japan	None	Chest pain	ITCZ	Survival
Shintani et al.[13]	56	F	Japan	Bronchiectasis	Sputum, fever	ITCZ	Survival
Goto et al.[14]	70	F	Japan	NTM	Sputum, chest pain	VRCZ	Survival
Masuo et al.[15]	58	F	Japan	NTM	Cough	VRCZ	Survival
Sekiguchi et al.[16]	65	F	Japan	RA, bronchiectasis	Cough, sputum	VRCZ	Survival
Li et al.[17]	52	M	China	None	Cough, sputum, hemoptysis	VRCZ, AMPH-B, PCZ	Survival
Watanabe et al.[18]	65	F	Japan	NTM, sinusitis	Cough, sputum	VRCZ	Survival
Watanabe et al.[18]	47	F	Japan	RA, NTM, sinusitis	Impaired sense of smell, nasal discharge	AMPH, VRCZ, ITCZ	Survival
Present case	66	M	Japan	NTM	Cough, sputum	None	Survival

Abbreviations: AMPH-B, amphotericin B; FLCZ, fluconazole; ITCZ, itraconazole; MCZ, miconazole; NTM, nontuberculous mycobacteria; Op, operation; PCZ, posaconazole; RA, rheumatoid arthritis; USA, United States of America; VRCZ, voriconazole; 5-FC, 5-fluorocytosine.

TABLE 2 Summary of the susceptibility of various antifungal agents for *Exophiala dermatitidis*.

Author (references)	MCFG	CPFG	AMPH-B	5-FC	FLCZ	ITCZ	VRCZ	MCZ
Barenfanger et al.[4]	NA	NA	NA	NA	NA	NA	NA	NA
Kenney et al.[5]	NA	NA	NA	NA	NA	NA	NA	NA
Mukaino et al.[6]	NA	NA	NA	NA	NA	NA	NA	NA
Taj-Aldeen et al.[7]	NA	NA	0.25	32	192	0.094	NA	NA
Ozawa et al.[8]	NA	NA	NA	NA	NA	NA	NA	NA
Tanamachi et al.[9]	16	NA	0.25	4	8	0.25	NA	0.125
Bulloch[10]	NA	NA	NA	NA	NA	NA	NA	NA
Suzuki et al.[11]	16	NA	2	4	64	2	1	1
Mukai et al.[12]	16	NA	0.5	1	8	0.25	0.12	0.12
Shintani et al.[13]	NA	NA	NA	NA	NA	NA	NA	NA
Goto et al.[14]	32	8	0.25	128	8	0.12	0.06	0.5
Masuo et al.[15]	16	16	0.5	2	16	0.5	0.125	0.25
Sekiguchi et al.[16]	16	NA	1	NA	NA	0.25	0.12	NA
Li et al.[17]	NA	NA	NA	NA	NA	NA	NA	NA
Watanabe et al.[18]	8	16	0.25	2	8	0.25	0.12	0.5
Watanabe et al.[18]	16	16	0.25	4	8	0.25	0.12	5
Present case	16	8	8	8	32	0.5	8	NA

Abbreviations: AMPH-B, amphotericin B; CPFG, caspofungin; FLCZ, fluconazole; ITCZ, itraconazole; MCFG, micafungin; MCZ, miconazole; NA, not available; VRCZ, voriconazole; 5-FC, 5-fluorocytosine.

spacer region in the ribosomal DNA revealed that the fungus was *E. dermatitidis*. The patient underwent a follow-up examination without receiving drug treatment at his request. His condition is stable at present.

DISCUSSION

E. dermatitidis is a melanized yeast-like organism that belongs to the dematiaceous family of fungi[19] and is one of causative pathogen of phaeophyphomycosis. In humans, the fungus is rare as a cause of fungal infections. The most commonly infected organ is the skin, and the most frequent type of deep infection is pulmonary infection.[19] Although several studies on *E. dermatitidis* pulmonary infections have been reported in CF patients, only 16 cases have been reported in non-CF patients.[4–18]

A summary of non-CF patients with *E. dermatitidis* pulmonary infections is presented in Table 1. Most patients were middle-aged and older females and were from Asia. Patients frequently had cough and sputum, but some also had hemoptysis (4/17) and fever (3/17). The patient described in the present case is also a Japanese in his 60s but not a female patient. He had cough and sputum, but there were no other symptoms such as fevers, sweats and weight loss for follow-up periods. It seems there are not specific symptoms for *E. dermatitidis* pulmonary infections, and it may be difficult to distinguish this infections from only patient's symptoms. Regarding the reported region, immunological differences in the host or differences in exposure to fungal propagules may affect disease progression.[11]

Many patients had bronchiectasis as an underlying disease (Table 1). In recent years, NTM complications have been reported more frequently.[14,15,18] Interestingly, previous cases did not report any immunocompromised patients, although immune status has proven to affect disease progression.[19] The present case was immunocompetent and complicated by NTM. A previous report showed that although prompt mucociliary and phagocytic clearance occurs in healthy lungs, anatomically abnormal and immunocompromised airways, such as those in bronchiectasis, are at a higher risk of fungal acquisition, colonization, and potential disease.[20] Additionally, the incidence and prevalence of NTM have increased worldwide.[21] Fujita et al. reported that approximately 45% of patients with *Mycobacterium avium-intracellulare* complex had chronic coinfection with pathogenic microorganisms, such as methicillin-sensitive *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Aspergillus* spp., among whom 85.1% had bronchiectasis.[22] It is unclear whether NTM infection is associated with *E. dermatitidis* infection in non-CF patients. On the other hand, Kondori et al. reported that serum levels of IgG antibodies to *E. dermatitidis* were significantly higher in the *E. dermatitidis* culture-positive CF patients compared to culture-negative CF patients.[23] CF patients with higher level of *E. dermatitidis* IgG antibodies were more often colonized with NTM.[23] It was also reported that CF patients with *E. dermatitidis* isolation had higher rates of NTM isolation compared to CF patients without *E. dermatitidis* isolation.[24] Currently, few reports on *E. dermatitidis* pulmonary infections in non-CF patients have been published. However, it has the potential to increase in the future with the increase in the number of patients with NTM infection.

Appropriate treatments for *E. dermatitidis* pulmonary infections have not yet been established. Previous cases were treated with monotherapy or combination therapy with amphotericin B (AMPH-B), 5-fluorocytosine, itraconazole (ITCZ), voriconazole (VRCZ), and other antifungals.[4–18] Several studies have demonstrated the susceptibility of various organisms to antifungal agents (Table 2). The minimum inhibitory concentrations of AMPH-B, ITCZ and VRCZ are low according to these studies, while those of micafungin, caspofungin, and fluconazole are relatively high. Our patient did not receive medical treatment for *E. dermatitidis* pulmonary infection. Antifungal susceptibility testing in this study also revealed that the minimum inhibitory concentration of ITCZ was low. Therefore, we intend to administer ITCZ if our patient's condition deteriorates. Further studies are needed to establish the treatment strategy for *E. dermatitidis* pulmonary infection.

The prognosis of *E. dermatitidis* pulmonary infection in patients without CF was good (Table 1), considering that only one death was reported.[7] The cause of death was cervical cancer progression and a complicated infection of *Candida krusei* fungemia, not *E. dermatitidis* pulmonary infection. Our patient's condition is stable at present. However, diseases caused by *E. dermatitidis* range from benign cutaneous infections to systemic infections, with a 40% fatality rate.[19] In addition, it was reported that a non-CF patient with *E. dermatitidis* pulmonary infection relapsed after 11 months of antifungal therapy.[16] Therefore, careful follow-up of this disease is necessary.

In conclusion, we described a rare case of pulmonary *E. dermatitidis* coinfection with NTM. The incidence of this infection may possibly increase with increased incidence of NTM infections. Additional research is needed because the treatment strategy for this infection has not been sufficiently clarified yet.

AUTHOR CONTRIBUTIONS

Writing-original draft: Seigo Miyoshi. *Writing review and editing*: Seigo Miyoshi, Miyuki Tanabe, Mayuko Semba, Chika Sato, Sanae Aoyama, Akira Watanabe, Ryoji Ito, Kumi Hamada, Akira Watanabe, Masahiro Abe. All authors have read and agreed to the published version of the manuscript.

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None declared.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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