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LETTER TO THE EDITOR

Coinfection of pulmonary nocardiosis and nontuberculous mycobacterial pulmonary disease in patients without known immunodeficiency

Dear Editor

Both pulmonary nocardiosis and nontuberculous mycobacterial pulmonary disease (NTM-PD) have been reported in immunocompromised or immunocompetent patients; however, few articles have reported their coinfection,[1—3] and most of them are in patients with immunodeficiency. Here, we present a case series of coinfection with pulmonary nocardiosis and NTM-PD in patients without known immunodeficiency, and describe the characteristics of this population.

From January 2017 to July 2021, NTM and *Nocardia* isolates were collected from respiratory tract samples, including the sputum, bronchial wash, bronchoalveolar lavage fluid (BALF), and lung biopsy specimens at our hospital. *Nocardia* was identified based on colony morphology and positive modified acid-fast staining. The species were further identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *Mycobacterium* was also identified by colony morphology and acid-fast staining. When the *M. tuberculosis* antigen test was negative, the species were further identified by universal 16s rRNA gene sequences to confirm the diagnosis of NTM. NTM-PD was diagnosed based on a combination of clinical, radiological, and microbiological features, as described by the American Thoracic Society Mycobacterial Disease Subcommittee.[4] Pulmonary nocardiosis was diagnosed when the patient had pulmonary symptoms, radiological abnormalities, and at least one positive culture from sputum, bronchial wash, BALF, or lung biopsy.

From 448 patients with NTM infection, *Nocardia* was isolated from 14. All 14 patients had pulmonary symptoms and radiographic opacities. According to the diagnosis definition, four patients were excluded because NTM was isolated from the sputum only once. Therefore, coinfection of pulmonary nocardiosis and NTM-PD were identified in 10 patients. All these patients were absent from active malignancy, human immunodeficiency virus infection, corticosteroid or immunosuppressive drug use, solid organ transplantation, or stem cell transplantation. The clinical data of these patients are summarised in Table 1.

The mean patient age was 59.2 ± 11.7 (range 45-84) years, with an apparent female predominance (female:male ratio 4:1). Bronchiectasis was noted in all patients, with chronic obstructive pulmonary disease (COPD) observed in 5/10 patients. Two patients had a history of smoking and one, alcohol abuse. No patient had diabetes mellitus or pulmonary tuberculosis.

All patients had NTM-PD first, with pulmonary nocardiosis diagnosed simultaneously or 2—20 months after NTM-PD. At the time of diagnosis of pulmonary nocardiosis, all patients exhibited cough and sputum production, followed by dyspnoea in 7/10 patients, haemoptysis in 6/10 patients, and fever in 3/10 patients. Both NTM and nocardiosis in all patients were confined to the lungs, without dissemination. The leading species were *Mycobacterium intracellular* in NTM-PD and *Nocardia otitidiscaviarum* and *Nocardia cyriacigeorgica* in pulmonary nocardiosis.

Chest computed tomography (CT) revealed diffuse bronchiectasis and opacities in all patients, along with nodules, masses, infiltrates, and consolidations. The nodules were centrilobular, and all patients showed a diffuse tree-in-bud appearance. Cavities were noted in the upper lobes or superior segment of the lower lobes of three patients. One patient showed atelectasis. No patient had pleural effusion.

All patients were treated medically for at least one year, followed-up for 1—3 years, and were all alive in March 2022. Patients with NTM-PD were mainly treated with rifampicin, ethambutol, and clarithromycin/azithromycin. Patients with pulmonary nocardiosis were mainly treated with levofloxacin/moxifloxacin ± minocycline. Only one patient was treated with sulfamethoxazole (TMPCO). Post-treatment, seven patients improved clinically and radiologically, two maintained stable symptoms and chest CT findings, and one progressed slowly, with new lesions on chest CT. Sputum cultures during follow-up were negative in 4/4 patients with NTM-PD and 6/7 patients with pulmonary nocardiosis.

NTM-PD is strongly associated with bronchiectasis. Previous studies showed that the rate of NTM-PD in non-cystic fibrosis bronchiectasis was 5%-30%[5]; however, the causal relationship between the two diseases has not been fully established. The risk of pulmonary nocardiosis is increased in immunocompromised patients, particularly in those with defects in cell-mediated immunity. However, patients with chronic lung diseases, such as COPD and bronchiectasis, also have an increased risk of *Nocardia* infection. Lower airway bacterial colonisation in chronic lung diseases has been

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Table 1 Clinical data of 10 patients with coinfection of pulmonary nocardiosis and nontuberculous mycobacterium pulmonary disease.

No. (Sex)	Species of NTM	Species of *Nocardia*	Time interval from NTM to nocardiosis	Treatment	Outcome	Sputum cultures during follow-up
1 (M)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	RFP+EMB+CLA+LEVO	3 years, progress slowly	NTM, NA; *Nocardia*, positive
2 (F)	*M. intracellulare*	*N. cyriacigeorgica*	Simultaneous	RFP+EMB+AZI+MOXI	2.5 years, improved	NA
3 (F)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	MOXI+MINO	1 year, improved	NA
4 (M)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	RFP+EMB+CLA+MOXI+MINO	2.5 years, improved	Negative
5 (F)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	RFP+EMB+CLA+MOXI+MINO	2 years, improved	NA
6 (F)	*M. intracellulare*	*N. cyriacigeorgica*	Simultaneous	RFP+EMB+CLA+TMPCO	1 year, improved	Negative
7 (F)	*M. abscessus*	*N. farcinica*	2 months	CLA+LEVO	1 year, stable	NTM, NA; *Nocardia*, Negative
8 (F)	*M. intracellulare*	*N. farcinica*	4 months	RFP+EMB+AZI	3 years, stable	Negative
9 (F)	*M. intracellulare*	*N. cyriacigeorgica*	2 months	RFP+EMB+CLA+LEVO	2 years, improved	Negative
10 (F)	*M. intracellulare*	*N. beijingensis*	20 months	RFP+EMB+CLA+LEVO+MINO	3 years, improved	NA

NTM: nontuberculous mycobacterium; RFP: rifampin; EMB: ethambutol; CLA: clarithromycin; LEVO: levofloxacin; AZI: azithromycin; MOXI: moxifloxacin; MINO: minocycline; TMPCO: compound sulfamethoxazole tablet; NA: not available.

suggested to alter ciliary motility and cause epithelial damage, thereby facilitating the presence of *Nocardia*.[6] Therefore, bronchiectasis may be a connecting link between pulmonary nocardiosis and NTM-PD in immunocompetent patients. Interestingly, no patient in our series had extrapulmonary nocardiosis or NTM infection, which may be associated with underlying immunocompetence, to restrict infections within the epithelial-damaged lungs.

TMPCO has been the traditional antimicrobial of choice for pulmonary nocardiosis but was administered to only one patient in this study owing to a confirmed or suspected drug allergy in other patients. Quinolone ± minocycline was the treatment of choice for most patients in this study, with most patients showing favourable outcomes, compared with the high mortality rate of approximately 40% reported in the literature.[6] The favourable outcomes may be due to the immunocompetent nature of the patients and the confined infection within the lungs. Sulfamethoxazole-free regimens with other sensitive medicines for pulmonary nocardiosis appeared to be effective in this population.

Authors' contributions

SXF and SHL contributed to the conception of the study. SXF, LWJ and LLL contributed to data collection, data analysis and interpretation. SXF, LWJ and SHL drafted the manuscript. All authors revised the manuscript for intellectual content and approved the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval and consent to participate

The study was approved by the Research Ethics Commission of Peking Union Medical College Hospital in accordance with the Declaration of Helsinki. Informed consents have been obtained from patients or their relatives.

Availability of data and materials

All the data will be available to other researchers on reasonable requests to the corresponding author after publication.

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