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【 CASE REPORT 】

Pneumococcal Pneumonia Co-infection with *Mycobacterium avium* and *Nocardia cyriacigeorgica* in an Immunocompetent Patient

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Abstract:
A 61-year-old woman was transferred with a complaint of a fever and productive cough. She had tested positive for *Mycobacterium avium* and *Nocardia cyriacigeorgica* at least twice, and *Streptococcus pneumonia* (PISP) was isolated (3+) from her purulent sputum. As radiological findings, a lower lung field-dominant infiltration shadow and nodular shadow with cavity were recognized in the bilateral lung fields. We diagnosed her with pneumococcal pneumonia co-infection with *M. avium* and *N. cyriacigeorgica*. She was treated with MEPM for pneumococcal pneumonia, a standard regimen containing clarithromycin for pulmonary *M. avium* complex (MAC) disease, and sulfamethoxazole/trimethoprim for pulmonary nocardiosis. She improved with appropriate treatment.

Key words: pneumococcal pneumonia, *Mycobacterium avium*, *Nocardia cyriacigeorgica*, co-infection

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Introduction

Nocardia species is an aerobic Gram-positive actinomycetes commonly found in soil and water. Pulmonary nocardiosis occurs mainly as an opportunistic infection in immunocompromised patients with human immunodeficiency virus (HIV) infection or receiving immunosuppressive treatments (1, 2). However, it sometimes occurs in immunocompetent patients with chronic pulmonary disease, such as chronic obstructive pulmonary disease (COPD) or bronchiectasis (3, 4).

Cases of pulmonary *Mycobacterium avium* complex (MAC) disease have recently increased in Japan (5), and it sometimes occurs in immunocompetent hosts without underlying diseases (6). There have been two reports of immunocompetent patients with pulmonary MAC disease complicated with pulmonary nocardiosis (7, 8).

To our knowledge, this is the first report of an immunocompetent patient with pulmonary MAC disease complicated with pulmonary nocardiosis caused by *Nocardia cyriacigeorgica* in the presence of pneumococcal pneumonia.

Case Report

A 61-year-old woman was transferred for investigation and treatment from another hospital (the second hospital she visited) with complaints of a fever and a productive cough. She had visited the first hospital with mild symptoms two months earlier, and a sputum culture examination of common bacteria and acid-fast bacilli had led to the isolation of *M. avium* and *M. avium* by MAC-polymerase chain reaction (PCR). However, her clinical symptoms were mild, so no treatments had been administered at the first hospital.

She was then introduced to a second hospital for an investigation and treatment one month ago, and another sputum culture examination of common bacteria and acid-fast bacilli had led to the isolation of *M. avium* and *Nocardia* species in that hospital. Because her clinical symptoms of a fever, productive cough, and general fatigue had worsened one week ago, she was introduced to our hospital (the third hospital she visited) for an investigation and treatment.

She had been administered ceftriaxone (CTRX) at 2 g/day for pneumonia and trimethoprim/sulfamethoxazole (TMP/

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Table 1. Laboratory Data on Admission.

Peripheral blood		Chemical screening			
WBC	13,520 /μL↑	TP	7.0 g/dL	pH	7,447
Neutrophils	83.1 %↑	Glu	106 mg/dL	$PaCO_2$	35.8 mmol/L
Lymphocytes	12.9 %↓	Bil (T)	0.2 mg/dL	PaO_2	84.3 mmol/L
Monocytes	3.8 %	ALP	259 mg/dL	BE	0.0
Basophils	0.2 %	Cho	179 mg/dL	HCO_3^-	23.2 mmol/L
RBC	398×10^4 /μL	γ-GTP	35 U/L↑	Lactate	1.97 mmol/L
Hb	12.0 g/dL	LDH	233 U/L↑		
Ht	35.4 %	Alb	3.0 g/dL↓	Serology	
Platelets	34.1×10^4 /μL	Glb	4.0 g/dL↑	Procalcitonin	0.25 ng/mL↑
PT	11.4 s	ChE	188 U/L↓	β-D-glucan	<6.0 pg/mL
APTT	28.8 s	ALT	34 U/L↑	*Cryptococcus* antigen	(-)
Fibrinogen	624 mg/dL↑	AST	42 U/L↑	*Aspergillus* antigen	(-)
		Crn	0.80 mg/dL	T-SPOT.TB	(-)
		BUN	10 mg/dL	MAC antibody	4.67 U/mL↑
		UrA	2.6 mg/dL		
		CRP	9.56 mg/dL↑		
		Na	134 mmol/L		
		K	4.4 mmol/L		
		Cl	96 mmol/L		

Table 2. Antimicrobial Susceptibilities of *Nocardia cyriacigeortica* Isolated from Sputum Culture.

Antibiotics	MIC (μg/mL)
Amikacin	1
Ceftriaxone	4
Ciprofloxacine	>4
Imipenem	1
Linezolid	2
Minocycline	2
Trimethoprim/Sufametoxazole	<4.75/0.25
Cefotaxime	4
Cefpirome	4
Gentamycin	<0.5
Ampicillin	>8
Clarithromycin	>8
Erythromycin	>2

SMX) at 8 g/day for pulmonary nocardiosis at the second hospital. However, because adverse reactions (gastrointestinal symptoms and eruption) appeared, the treatment was stopped three days later, and afterwards, she was followed up.

Her occupation was a healthcare worker, and she had not had any marked exposure to environments rich in soil. She had no smoking history. She had a history of pulmonary MAC disease 12 years ago and had received chemotherapy for 1 year. Afterwards, because had condition had improved and she had no symptoms, sputum culture examinations were not performed, and no follow-up had been conducted. She had no history of HIV, diabetes mellitus, or solid organ transplantation. She had not received inhaled or systematic corticosteroids or any immunosuppressive agents.

On a physical examination, her body weight and height were 42 kg and 156 cm. Chest auscultation revealed coarse crackles in the right lower lung field. Regarding laboratory findings, the inflammatory response was positive, her white blood cell count was 13,520/μL, and her C-reactive protein level was 9.56 mg/dL. Although mild hypoalbuminemia was noted, her serum globulin level was slightly elevated. Mild liver dysfunction was recognized. Procalcitonin showed mild elevation to 0.25 ng/mL, and a urinary pneumococcal antigen test showed a positive response. MAC antibody showed a positive response (4.67 U/mL), but an interferon-gamma release assay (IGRA) showed a negative response (Table 1).

Gram staining of the sputum showed branching Gram-positive filaments, and the culture grew *Nocardia* species several times at the previous hospital and our hospital. The isolates were identified as *N. cyriacigeorgica* using 16S ribosomal ribonucleic acid (RNA) gene sequencing by the Medical Mycology Research Center of Chiba University. Minimal inhibitory concentrations (MICs) for selected antimicrobial agents were determined by the broth microdilution method following the guidelines of the Clinical and Laboratory Standard Institute (9) (Table 2); the isolates were susceptible to TMP/SMX. However, Gram staining of the sputum showed Gram-positive cocci, and the purulent culture grew *Streptococcus pneumoniae* (3+). Because *S. pneumoniae* isolated from this patient showed intermediate resistance to penicillin G (MIC: 0.5 μg/dL), we judged Penicillin-intermediate *S. pneumoniae* (PISP) according to the Clinical and Laboratory Standards Institute (CLSI) definition of susceptibility. Acid-fast staining of the sputum was positive, and *M. avium* (CAM MIC: 0.25 μg/dL) was identified several times by DNA-DNA hybridization (DDH) methods.

Regarding the radiological findings, chest computed to-

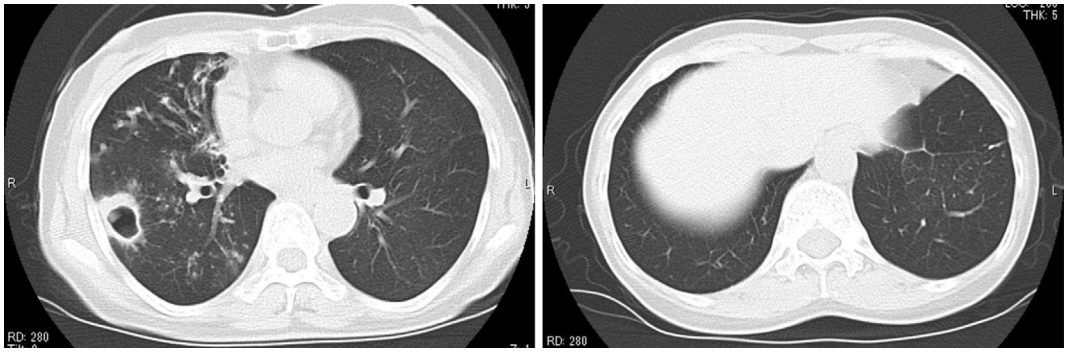

Figure 1. **Chest CT showed small nodular shadows with bronchiectatic change in the right middle and lower lobes and cavity lesions in the right S^6 segment (A, B) (one month ago at the previous hospital).**

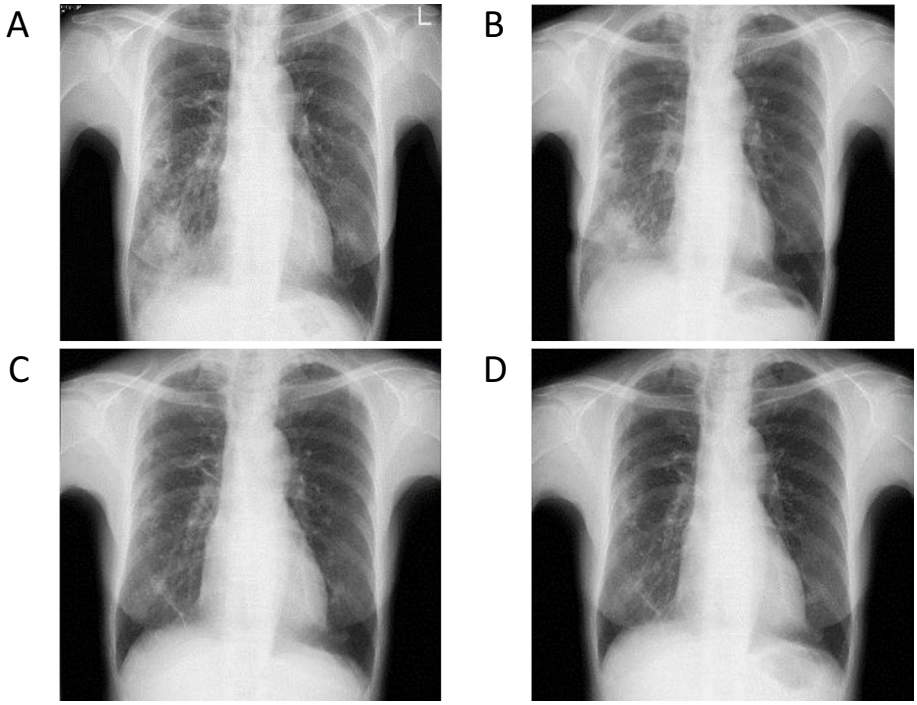

Figure 2. **Chest X-ray on admission to our hospital showed infiltration shadows with cavities (arrow) in the middle and lower lung fields and left lower lung fields (A). Chest X-ray after one month revealed a slight improvement (B), that after six months revealed the marked improvement of infiltration shadows with cavities in the right middle and lower lung fields and left lower lung fields (C), and that after one year revealed no notable changes (D).**

mography (CT) one month ago at the second hospital had shown small nodular shadows with bronchiectatic changes in the right middle and lower lobes and cavity lesions in the right S^6 segment (Fig. 1A, B). Chest X-ray and chest CT on admission showed the deterioration of small nodular shadows with bronchiectatic changes in the right middle and lower lobes and left lingula lobes but similar findings for cavity lesions in the right S^6 segment. Furthermore, a new infiltration shadow appeared in the right lower lung field on chest X-ray and in the right S^8 segment on chest CT on admission (Fig. 2A, 3A, B). Finally, we diagnosed her with pneumococcal pneumonia co-infected with *M. avium* and *N. cyriacigeorgica* in combination with the information from the previous hospital.

Regarding the treatment in our hospital, because she showed adverse reactions to CTRX and/or TMP/SMX in the previous hospital, we initiated treatment using meropenem (MEPM) at 3 g/day for pneumococcal pneumonia and pulmonary nocardiosis and combined chemotherapy using rifampicin (RFP) at 300 mg/day, ethambutol (EB) at 500 mg/day, clarithromycin (CAM) at 600 mg/day, and streptomycin (SM) at 0.5 g/3 times per week for pulmonary MAC disease. Because her clinical symptoms of a fever and productive cough and the inflammatory response were improved 14 days after admission, we completed the treatment with MEPM and added treatment using a decreased dose of

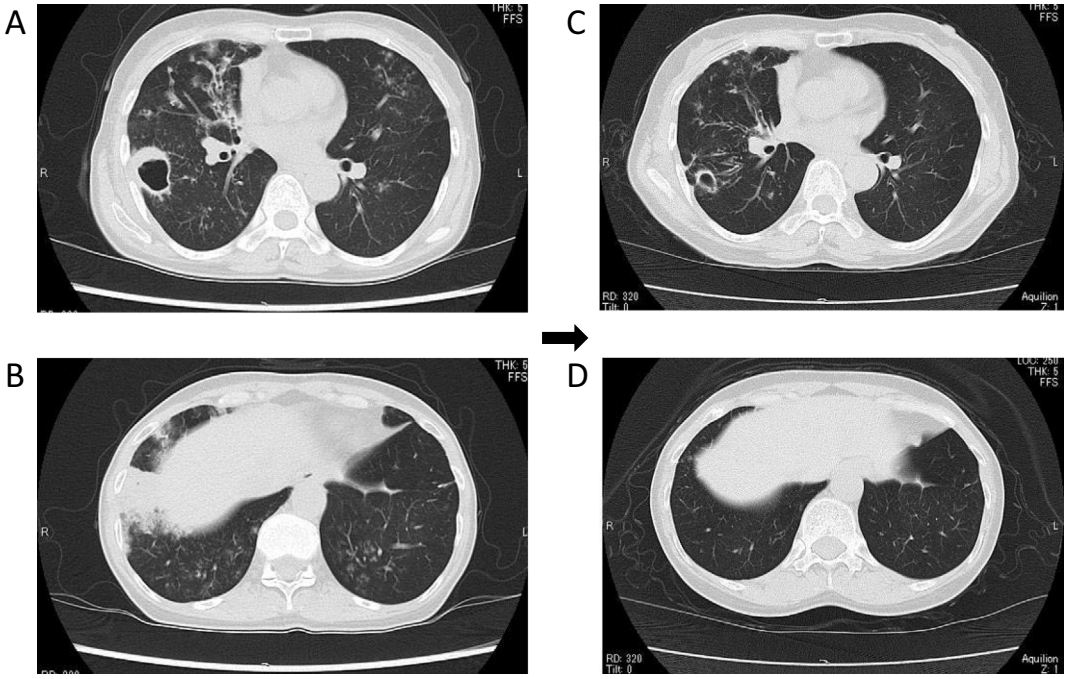

Figure 3. **Chest CT on admission revealed small nodular shadows with bronchiectatic changes in the right middle and lower lobes and left lingula lobes and a cavity lesion in the right S^6 segment (A) and an infiltration shadow in the right lower lobe (B). Chest CT one year after the initiation of treatment showed an improvement of small nodular shadows and infiltration shadows containing the cavity lesion, except for bronchiectatic changes (C, D).**

TMP/SMX at 6 g/day for pulmonary nocardiosis, considering the possibility of the appearance of adverse reactions. Chest X-ray on discharge showed a slight improvement (Fig. 2B). We continued TMP/SMX for six months, and thereafter, only standard chemotherapy for pulmonary MAC disease was continued, with planned continuation for two years (Fig. 4).

Chest X-ray at six months after the initiation of treatment using TMP/SMX and combined chemotherapy for pulmonary MAC disease showed significant improvement of the infiltration shadow with cavity lesions in the right middle and lower lung fields and left lower lung field (Fig. 2C). Chest X-ray (Fig. 2D) and chest CT (Fig. 3C, D) showed improvement of the small nodular shadows and infiltration shadows containing a cavity lesion, except for bronchiectatic changes, after one year.

Discussion

Nocardia species are Gram-positive aerobic bacilli that cause respiratory tract infections in around 50% to 70% of nocardiosis patients (9). Pulmonary nocardiosis most frequently occurs in immunocompromised patients with solid organ transplantation, hematopoietic stem cell transplantation, HIV infection, or corticosteroid treatment (1, 2). However, it is also known to occur in immunocompetent patients with underlying pulmonary diseases, such as chronic obstructive pulmonary disease and bronchiectasis (3, 4). In our case, because *N. cyriacigeorgica* had been simultaneously isolated several times from the bronchiectatic or cavity lesion formed by pulmonary MAC disease, and because *S. pneumoniae* had infected these lesions, a diagnosis of pneumococcal pneumonia co-infection with pulmonary nocardiosis and pulmonary MAC disease in an immunocompetent patient was made. Such bronchiectatic and cavity lesions due to MAC cause respiratory immune defense system dysfunction and facilitate lower respiratory tract infections and bacterial colonization. Furthermore, bacterial colonization alters ciliary motility, causes epithelial damage, and facilitates nocardia infection (10).

Nocardia species were recently classified into several different species by 16S ribosomal RNA sequencing. *N. cyriacigeorgica* was the first to be identified and classified as a new species by Yassin et al. in 2001 (11). According to a recent study using 16S ribosomal RNA sequencing, although *N. asteroides* is the most frequently isolated in Australia (12), *N. cyriacigeorgica* was the most frequently isolated strain in Taiwanese and Spanish patients with pulmonary nocardiosis (13, 14). A difference in the local distribution of *Nocardia* strains may exist. Because pulmonary *N. cyriacigeorgica* disease shows a notable pattern compared with other nocardia infections (13), a large-scale world population study of pulmonary *N. cyriacigeorgica* disease should be performed to examine the clinical characteristics in the future.

Several reports have described *Nocardia* species co-infection with other microorganisims in immunocompromised hosts or immunocompetent hosts with underlying

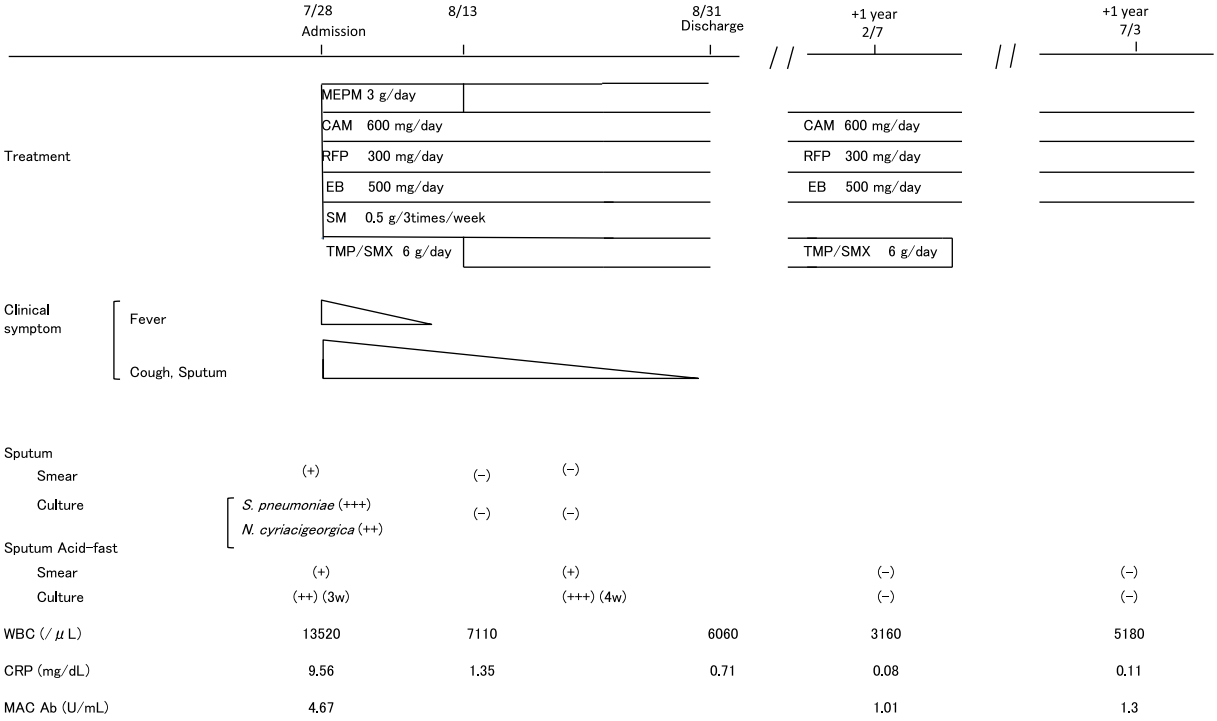

Figure 4. Clinical course of pneumococcal pneumonia co-infected with *Mycobacterium avium* and *Nocardia cyriacigeorgica*.

respiratory disease. *Nocardia* species co-infection with *Aspergillus* species was found to be the most frequent in previous reports (12, 13). In our case, three microorganisms (*N. cyriacigeortica*, *M. avium*, and *S. pneumoniae*) were isolated simultaneously on admission to our hospital. Although the complication rate of pulmonary MAC disease in patients with pulmonary nocardiosis was 6% in previous reports (12), and 5 previous reports described pulmonary nocardiosis co-infected with pulmonary MAC disease in immunocompromised or immunocompetent hosts (7, 8, 15-17), to our knowledge, this is the first report of 3 microorganisms isolated several times simultaneously, necessitating individual treatment for pneumococcal pneumonia, pulmonary nocardiosis, and pulmonary MAC disease. Regarding the radiological findings of pulmonary nocardiosis in an immunocompetent patient, Fujita et al. reported that it often showed a nodular-bronchiectatic pattern resembling typical radiological findings in middle-aged women with pulmonary NTM disease (18). Because pulmonary nocardiosis and pulmonary NTM disease are similar with regard to several clinical findings in immunocompetent patients, pulmonary nocardiosis in an immunocompetent patient might be misdiagnosed as pulmonary NTM disease. We must therefore practice caution in cases showing mixed infection due to multiple microorganisms, especially in immunocompetent patients with underlying respiratory diseases, and perform multiple microbiological examinations to obtain a correct diagnosis.

Concerning the treatment of this patient in our hospital, because clinical symptoms of a fever and productive cough and positive inflammatory response with leukocytosis were recognized, and adverse reactions to CTRX and/or TMP/SMX appeared at the previous hospital, we first performed antibiotic therapy for bacterial infection due to PISP and pulmonary nocardiosis using MEPM as carbapenem antibiotics (imipenem/cilastatin was not available in our hospital) for two weeks. Furthermore, as this patient also showed radiological findings of small nodular shadows with bronchiectatic changes leading to the suspicion of progressing pulmonary MAC disease on admission, we initiated combined chemotherapy using CAM, RFP, and EB including SM simultaneously. The clinical symptoms and inflammatory response gradually improved with treatment.

As favorable susceptibility of *N. cyriacigeortica* to TMP/SMX (Table 2) was obtained, we administered a decreased dose of TMP/SMX for pulmonary nocardiosis, considering future outpatient treatment, and fortunately, no adverse reactions were noted. We selected treatment including SM for pulmonary MAC disease with a cavity according to the guideline of the American Thoracic Society (ATS) (19). TMP/SMX is the first recommended drug therapy for pulmonary nocardiosis. As alternative drugs, amoxicillin/clavulanic acid, minocycline, imipenem/cilastatin, amikacin, and ceftriaxone are effective against *Nocardia* species (10). However, as drug susceptibilities differ by *Nocardia* species, we had to identify the specific *Nocardia* species using molecular and biochemical analyses and drug sensitivity examinations. Sorrell et al. stated that the duration of treatment for pulmonary nocardiosis in an immunocompetent patient with underlying pulmonary disease should be at least six months. We thus administered TMP/SMX 6 g/day for 6 months according to that report (20).

Regarding the prognosis associated with *Nocardia* species

infection, the incidence of death due to pulmonary nocardiosis was better than that due to disseminated or cerebral nocardiosis with TMP/SMX. Although the present patient had a mixed infection due to *N. cyriacigeortica*, MAC, and *S. pneumonia* in an immunocompetent host with underlying respiratory disease, her condition improved with appropriate treatment without marked adverse reactions.

In conclusion, we reported the first case of pneumococcal pneumonia in a patient co-infected with pulmonary MAC disease (*M. avium*) and pulmonary nocardiasis (*N. cyriacigeortica*). We must practice care when encountering cases of infectious diseases due to multiple causative microorganisms in immunocompetent patients with underlying respiratory disease, and several microbiological examinations should be conducted in order to obtain a correct diagnosis.

The authors state that they have no Conflict of Interest (COI).

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