Letter to the Editor

Organizing pneumonia due to pulmonary non-tuberculosis mycobacteria: a case description and literature analysis

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Introduction

Infection is the main cause of organizing pneumonia (OP) (1); secondary organizing pneumonia (SOP) due to lung infection is reported to result from various pathogens, such as bacteria (2), fungi (3), and viruses (4). However, descriptions of SOP due to pulmonary nontuberculous mycobacteria (NTM) are rare, and only 10 cases have been reported. Here, we report one case of SOP due to NTM and review the relevant literature.

Case presentation

A 24-year-old man was admitted with a 2-month history of coughing and sputum production. He had no basic diseases or smoking history. Chest computed tomography (CT) showed a partially oval lesion with an incomplete consolidation ring on the anterior surface, central irregular cavity, and posterior surrounding consolidation in the right upper lobe (RUL), without any other lesions (*Figure 1*). The laboratory investigations including blood analysis of infection index, serum tumor markers, serum autoantibodies, blood cultures, and viral serologies were within the normal limits. Bacterial, mycobacterial, and fungal bronchoalveolar lavage fluid (BALF) samples were negative. He underwent bronchoscopy including in the RUL; however, no definitive sputum acid-fast bacilli (AFB) were detected on culture or polymerase chain reaction (PCR). The metagenomic next-generation sequencing (mNGS) on BALF samples showed *Mycobacterium xenopi* (the sequence number is 10) which constitutes a very rare and unusual lung infection. According to the NTM diagnostic guidelines (5), NTM can be diagnosed with positive molecular biological detection of BALF. To make a definitive diagnosis, the patient underwent a repeat bronchoscopy with lavage. The strain identification of the lavage fluid showed: *Mycobacterium xenopi*. The patient was diagnosed with NTM (*Mycobacteria xenopi*) and received anti-NTM treatment (treatment regimen: clarithromycin 500 mg/day, moxifloxacin 400 mg/day, ethambutol 750 mg/day, rifabutin 450 mg/day). Two weeks later, the patient's cough was unaccompanied by sputum. According to chest CT, the lesion in the RUL had improved, but a focal rounded area of ground-glass opacity (GGO) surrounded by a complete ring of consolidation in both lower lobes (LL) was observed, a typical manifestation of "reversed halo sign" in LL (*Figure 2*). A CT-guided lung biopsy in the LL and histopathological examination showed OP without granuloma and a positive AFB (*Figure 3*). These findings suggested that the progression of lesions in bilateral lungs was SOP due to *Mycobacteria xenopi* infection; the patient received anti-NTM treatment continually with a combination of prednisolone at a dose of 40 mg/day for 2 weeks. Oral prednisolone was tapered over a period of 6 months and withdrawn, the patient's symptoms and the opacity improved rapidly, the LL lesion was completely absorbed, and the RUL cavity also improved (*Figure 4*).

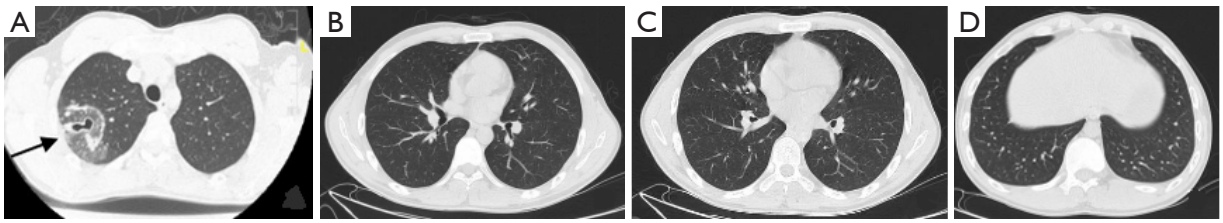

Figure 1 Case 1, initial chest CT showed partially oval lesion with a ring of consolidation on the anterior surface and a central cavity with surrounding consolidation in RUL (A, black arrow), without any other lesions (B-D). CT, computed tomography; RUL, right upper lobe.

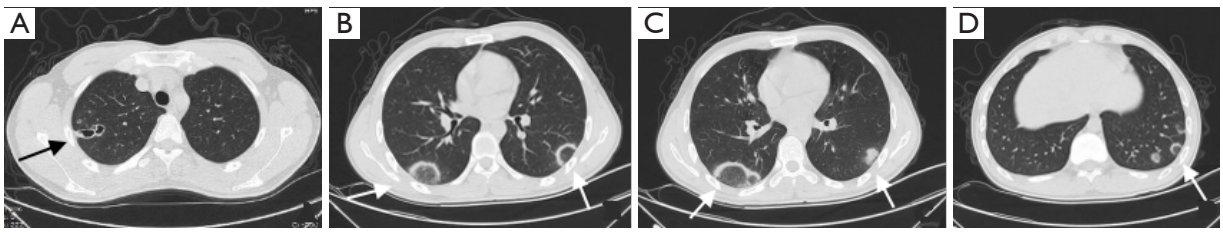

Figure 2 Case 1, first follow-up chest CT showed the improvement of the oval lesion and consolidation in RUL with no significant changes of the irregular cavity (A, black arrow). And showed focal rounded area of ground-glass opacity surrounded by a complete ring of consolidation in LL, a typical aspect of "reversed halo sign" (white arrows in B-D). CT, computed tomography; RUL, right upper lobe; LL, lower lobe.

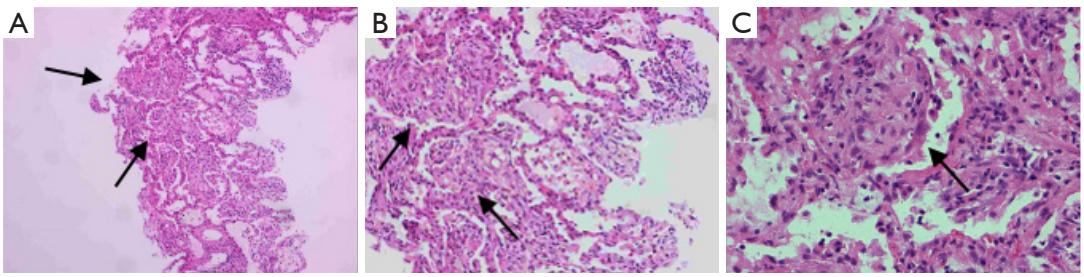

Figure 3 Case 1, pathological findings from LL biopsy with different magnifications (A: ×100; B: ×200; C, ×400) showing organizing pneumonia, non-granulomatous (black arrows, H&E staining). LL, lower lobe; H&E, hematoxylin and eosin.

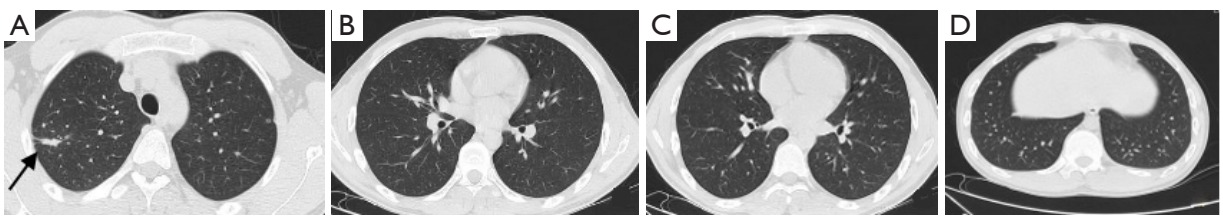

Figure 4 Case 1, second follow-up chest CT, showing absorption of the irregular cavity in RUL (A, black arrow), and also of the lesions in LL (B-D). CT, computed tomography; RUL, right upper lobe; LL, lower lobe.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Methods

To clarify the clinical and radiological features of patients with SOP due to NTM, we reviewed the literature about SOP due to NTM in the databases of PubMed and Wanfang from January 2000 to December 2023 and excluded the laboratory's basic studies related to SOP secondary to NTM.

Results

Including our one case, 11 cases were identified in the literature, among whom there were 6 males and 5 females, were mainly middle-aged and elderly patients (50–85 years old), and only 1 patient was a young adult patient (24 years old). Among the 11 patients, the main clinical symptoms included dyspnea in 6 cases, both fever and cough in 4 cases, weight loss in 2 cases, and chest pain in 1 case. Most patients had clinical complications with underlying diseases, including 3 patients with chronic obstructive pulmonary disease (COPD), 2 with cardiovascular and cerebrovascular diseases, 2 with surgical history, 1 with autoimmune disease who was taking hormones and immunosuppressants, and 1 with diabetes. In the chest imaging manifestations, there were 3 patients with multiple patchy exudation in 1 lung or both lungs, 3 patients with consolidation, 1 with GGO, 1 patient with honeycomb, and 1 with cavity, among which 2 cases were complicated with pleural effusion. Among the results of etiology examination, 4 cases were *Mycobacterium avium*, and 4 cases *Mycobacterium abscessus*, whereas *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium gordonae* (1 case) were rare. Histopathologic findings revealed that the lesions were distributed in patches with the small airways as the central focus, with patchy filling of alveoli and bronchioles by loose plugs of connective tissue, which was consistent with OP (6). All patients were cured after anti-NTM therapy combined with hormone therapy. The details are summarized in *Table 1*.

Discussion

OP is a pattern of lung-tissue repair after injury. It can be cryptogenic or a response to a specific lung injury and is also observed histopathologically in many diverse clinical contexts (16). OP is divided into 2 types, cryptogenic OP (COP) and SOP, according to the cause of disease (17). In addition to COP form, SOP can be induced by various causes, such as lung infection (3), collagen vascular diseases, drugs, or inhalation (17). As the diagnostic methods for NTM have advanced, the incidence of NTM lung disease is increasing worldwide. However, OP due to mycobacteria NTM has rarely been reported. From 2000 to December 2023, only 10 cases were reported; including the 1 case reported here, the total number of cases is 11.

Clinically, both men and women can experience this disease, although mostly middle-aged and elderly patients are affected. These patients experience constitutional symptoms such as weight loss, fever, malaise, cough and hemoptysis; the clinical symptoms are similar to those of the other respiratory diseases such as COPD, community-acquired pneumonia (CAP), and tuberculosis (TB). Most patients have certain high-risk factors, and the most common diseases are COPD and cardiovascular disease. It has been reported (18) that immunocompromised patients, particularly those with acquired immune deficiency syndrome, have an increased susceptibility to NTM infection and are partly responsible for the increasing prevalence of SOP by NTM infections. The pathogen in NTM-induced OP was *Mycobacterium avium*-intracellulare (MAC), followed by *abscessus*, and these are the most prevalent pathogens (9).

During the treatment of case 1, improvements were noticed in the RUL lesions following NTM treatment but also worsening lesions were observed in the bilateral LL. We thought that the worsening lesions in the bilateral LL were due to the progress of the NTM, not drug-induced pneumonitis. Firstly, the drugs used to treat NTM are not common drugs that induce OP (19). Also, Hirama *et al.* reported that nodules, bronchiectasis, and cavity formation were common radiological features in patients with NTM (20). According to the NTM diagnostic guidelines, the drug remained unchanged throughout the NTM treatment. So, during the process of the treatment in case 1, the drugs used to treat NTM were unchanged, only the prednisolone was gradually decreased. Upon review after 6 months, the patient's symptoms and the opacity had

Table 1 Cases of SOP due to NTM infection

Number	Sex	Age (years)	Basic diseases	Symptoms	Imaging manifestations	Pathological findings	Type of mycobacterial	Treatment	Outcome relapse of OP	References
1	Female	64	Arterial hypertension, rheumatic mitral valvular disease	Fever	Micronodules, tree-in-bud pattern, tubular bronchiectasis, and small consolidations with peripheral, basal and bilateral distribution	Thickened alveolar septa with lymphocytes and histiocytes and intraluminal plugs, composed of granulation tissue and fibroblasts	MAC	R + E + CAM + PSL 30 mg/day	Cure	Fernandes *et al.* (7)
2	Female	67	Operations	Fever and dyspnea	Patchy, widely dispersed air-space consolidations and GGO	Granulation tissues within alveolar ducts and peripheral airspaces, hyalinous exudates organized within peripheral airspaces, and mild alveolar thickening with edematous changes	MAC	R + E + CAM + PSL 30 mg/day	Cure	Hamada *et al.* (8)
3	Male	73	No	Fever	Infiltrates with an air bronchogram in the right upper lobe, and ground glass opacities in both lung fields	Epithelioid cell granuloma and OP	MAC	R + E + CAM	Cure	Nakahara *et al.* (9)
4	Female	66	No	Cough and fever	Multiple cavitary nodules	OP	*Abscessus*	R + CAM	Cure	Nakahara *et al.* (9)
5	Female	51	Chronic gastric reflux	Cough, chest pain and weight loss	Poorly defined nodular opacities in the inferior right upper lobe and a pronounced nodular consolidation in the right mid zone	Necrotizing granulomatous inflammation, caseous necrosis and auramine-positive tubercle bacilli in association with an OP	*Mycobacterium goodii*	AMK and meropenem ciprofloxacin and doxycycline	Cure	Waldron *et al.* (10)
6	Male	59	COPD	Dyspnea	GGO and consolidation mainly in the left upper lobe	Infiltration of inflammatory cells, mainly lymphocytes, and Masson body	*Abscessus*	PSL 30 mg/day	Cure	Watanabe *et al.* (11)
7	Female	85	RA, hypertension, COPD	Cough and dyspnea	The right upper, the right lower lobes and bilateral pleural effusions	Intra-alveolar young fibrosis tissue and granulocytic infiltrate, consistent with OP	*Kansasii*	HRE + PSL 60 mg/day	Cure	Starobin *et al.* (12)
8	Female	58	COPD, hypertension, transient ischemic attacks and coronary artery disease	Dyspnea, cough, weight loss	Cavitating consolidation at the left apex with widespread emphysema and bilateral lower lobe consolidation with air bronchograms	TBLB: inflamed, ciliated bronchial epithelium with alveolar spaces obliterated by a polypoid cellular combination of fibroblasts, inflammatory cells and foamy macrophages typical of OP without granulomas	MAC	HRE + PSL 40 mg/day	Cure	Jones *et al.* (13)
9	Female	50	A total gastrectomy for gastric cancer	–	Consolidation, centrilobular shadows, GGO and cavities	Non-necrotizing granuloma surrounded by infiltrative lymphocyte-dominant inflammatory cells	*Abscessus*	PSL 30 mg/day	Cure	Okazaki *et al.* (14)
10	Female	67	Diabetes mellitus and degenerative arthritis	Dyspnea and fever	Ill-defined multifocal consolidations with bronchial wall thickening and air-bronchogram in both lungs	PCNB specimen showed interstitial fibroblast infiltration with collagen deposition and multiple foci of fibroblastic plugs and non-necrotizing epithelioid cell granuloma	*Abscessus*	AMK, cefoxitin, and azithromycin + PSL (1 mg/kg/day)	Cure	Hong *et al.* (15)
11	Male	24	No	Cough	Irregular void with surrounding consolidation shadows, “reversed halo sign” in both the lower lobe	OP without granuloma and a positive AFB	*Mycobacterium xenopi*	H + R + E + PSL 30 mg/day	Cure	The present case

SOP, secondary organizing pneumonia; AMK, amikacin; CAM, clarithromycin; COPD, chronic obstructive pulmonary disease; E, ethambutol; GGO, ground-glass opacity; H, isoniazide; MAC, *Mycobacterial avium*-intracellulare; NTM, non-tuberculous mycobacteria; OP, organizing pneumonia; PCNB, percutaneous needle biopsy; PSL, predonizolone; R, rifampicin; RA, rheumatoid arthritis; TBLB, transbronchial lung biopsy; AFB, acid-fast bacilli.

improved rapidly, the LL lesion was completely absorbed, and the right upper lung cavity had also improved. If drug-induced pneumonitis was a contributing factor, the condition would have worsened and intensified, so OP caused by anti-NTM drugs was also ruled out.

There is currently sufficient literature describing the radiological features of NTM. Some features such as thin-walled cavity and bronchiectasis (21,22) in the middle lobes and the left upper lobe are typical NTM imaging features, as are other such as consolidation, GGO, nodules and "tree-in-bud" pattern and so on (9). However, SOP due to NTM is combined with imaging changes in areas such as near the periphery of LL, and "reversed halo sign" (23), especially during NTM treatment. During treatment of NTM, factors such as lesion progression and the presence of Interstitial lesions in LL should alert the clinician to consider the possibility of SOP by NTM.

The relationship between the NTM pathogens and the onset of SOP is still unknown; the occurrence of pathological reactions in TB is inextricably linked with the host's response to the invading NTM. Histologically, NTM exhibits granulomas with varying degrees of necrosis (24), but some studies have reported that NTM disease is sometimes accompanied by OP histologically. Yasuharu *et al.* (9) reported in their study of 98 NTM patients who had undergone a biopsy or surgical resection, 11 patients had OP that was revealed histologically. After excluding 6 patients who had OP-related diseases (idiopathic interstitial pneumonia, rheumatoid arthritis, etc.), the remaining 5 patients were SOP due to NTM. Marchevsky *et al.* (24) reported in their study of *Mycobacteria*-positive open-lung biopsy specimens from 40 patients that the specimens of 3 patients with bilateral diffuse infiltrating shadows and no underlying conditions exhibited OP histologically, which all suggested that NTM disease and OP may show no absolute limit in histologically, and it is difficult to clarify the NTM or OP for which they can coexist in histologically. In clinical practice, it is difficult to distinguish the secondary complications solely based on the course of disease; further diagnosis and treatment techniques are still needed to identify the etiology of the disease in clinical practice.

Although the use of corticosteroids in SOP has been and remains controversial, from the literature and our cases, we found that adding corticosteroids to the regimen led to a remarkable improvement, and that complete cure was achieved after corticosteroids were added to anti-TB therapy and the prognosis was good in most of the cases of COP. As the NTM chest disease is increasing worldwide, pulmonologists might have a greater opportunity to observe the NTM lung disease with OP. Additional studies are needed to improve the outcomes of patients with SOP due to NTM; SOP due to NTM should be considered during treatment when antibiotics and/or anti-mycobacterial drugs are not effective.

Conclusions

SOP due to NTM should be considered during treatment when antibiotics are not effective, especially during the treatment of lesion progression.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-193/coif). All authors report that this work was supported by the Nanjing Health Science and Technology Development Special Fund (grant number: M2021073). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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