

The Advance and Clinical Practice on Lung Disease Caused by *Mycobacterium abscessus*

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Abstract: *Mycobacterium abscessus* (*M. abscessus*) lung disease has gradually become a common clinical condition, with its incidence rate continuously rising, especially among patients with weakened immune function or those with chronic lung diseases. Given the high resistance of *M. abscessus* to antibiotics, the options for antibiotics are very limited. Additionally, long treatment times and poor patient compliance lead to low cure rates and high recurrence rates, making it one of the significant public health challenges threatening global health. This article presents two cases of patients diagnosed with *M. abscessus* lung disease using next-generation metagenomic sequencing technology. It reviews and analyzes the current research on *M. abscessus* along with details from these cases. Furthermore, this article emphasizes the necessity of timely, regular, and comprehensive treatment for *M. abscessus* lung disease. Meanwhile, we call for the formulation of robust prevention strategies, the optimization and innovation of treatment regimens, and the enhancement of follow-up management after cure to improve the understanding and handling capabilities of *M. abscessus* lung disease, thereby addressing the increasing clinical challenges.

Keywords: nontuberculous mycobacteria, *Mycobacterium abscessus* lung disease, clinical manifestations, diagnosis, treatment, prevention

Introduction

Nontuberculous mycobacteria (NTM) refer to a large group of mycobacteria excluding the *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*.¹ So far, more than 190 strains of NTM have been discovered,² and a small number of NTM are pathogenic, which can lead to infections in various tissues of the human body, including skin soft tissue, breast, eyes, musculoskeletal system, heart, lymphatic system, and tendon sheaths.^{3–6} Lung infections are particularly common.³ In the state of Hawaii, USA, the prevalence can be as high as 396 cases per 100,000 people.⁷ According to the growth rates of NTM, they are divided into two main categories: slow-growing and fast-growing species. Among the fast-growing species, *M. abscessus* is considered the most pathogenic.⁸ It is known that *M. abscessus* has three subspecies: *Mycobacterium abscessus* subspecies abscessus (MAB), *Mycobacterium abscessus* subspecies massiliense (MMA), and *Mycobacterium abscessus* subspecies bolletii (MAO).⁹ According to some reports, lung infections caused by *M. abscessus* make up 2.6–13% of NTM lung infections,^{10,11} especially in patients with weakened immune systems or chronic lung diseases, who face a higher risk of infection. The clinical manifestations of lung infection caused by *M. abscessus* are very similar to those of pulmonary tuberculosis, including cough, producing sputum, weight loss, pleural effusion, dyspnea, and hemoptysis. Additionally, due to a previous lack of understanding about this strain and the lack of easy and practical ways to identify the strain, it is easy to miss or misdiagnose the disease,¹² which can result in treatment failures. Simultaneously, *M. abscessus* exhibits complex resistance mechanisms encompassing target site modification, mutations at target loci, β -lactamase-mediated drug inactivation, activation of efflux pump systems, and cell wall permeability barriers.^{13,14} Consequently, the American Thoracic Society (ATS) recommends combination therapy with 3–4 active agents selected through in vitro susceptibility testing to prevent acquired resistance during

treatment, particularly against macrolides.⁹ However, specific regimens require comprehensive integration of pharmacokinetic/pharmacodynamic (PK/PD) characteristics, drug synergism, adverse effects, and multidimensional considerations including patient-specific factors (advanced age, obesity), comorbidities, and disease severity. Therefore, no standardized combination therapy protocol currently exists. Additionally, the treatment duration is long, and patient compliance is poor, making clinical treatment extremely challenging.^{12,15} *M. abscessus* lung disease has become one of the significant public health issues threatening human health.^{12,16,17}

Due to factors such as the unique biological characteristics of the pathogenic bacteria, the immune status of the host, the external environment, destruction of lung structure, and incomplete treatment,¹⁸ the recurrence rate of patients infected with *M. abscessus* may be as high as 40%,¹⁹ with a co-infection rate of aspergillus between 3.9% and 16.7%,¹⁸ which increases patient mortality. Therefore, it is essential to place a high emphasis on follow-up management after recovery. The purpose of this article is to explore the clinical characteristics, diagnosis, treatment, follow-up, prevention, and future research directions of *M. abscessus* lung disease through clinical practice and literature review, in order to help clinicians gain a comprehensive understanding of *M. abscessus* pulmonary disease and provide a useful reference for similar cases.

Cases Presentation

Case I

A 58-year-old female was admitted to our hospital on November 3, 2022, due to “persistent cough with purulent sputum for 2 years, worsening for 10 d”. She has a history of pulmonary tuberculosis for over 30 years and has been cured. A chest CT at the outpatient showed widespread small patchy spots in both lungs, particularly prominent in the basal segments of the lower lobes of both lungs and the middle lobe of the right lung, with local bronchial dilatation (Figure 1A). Next-generation metagenomic sequencing (mNGS) of sputum and bronchoalveolar lavage fluid (BALF) revealed MAB, inducing macrolide-resistant strains (Table 1). But the treatment was delayed because of the COVID-19

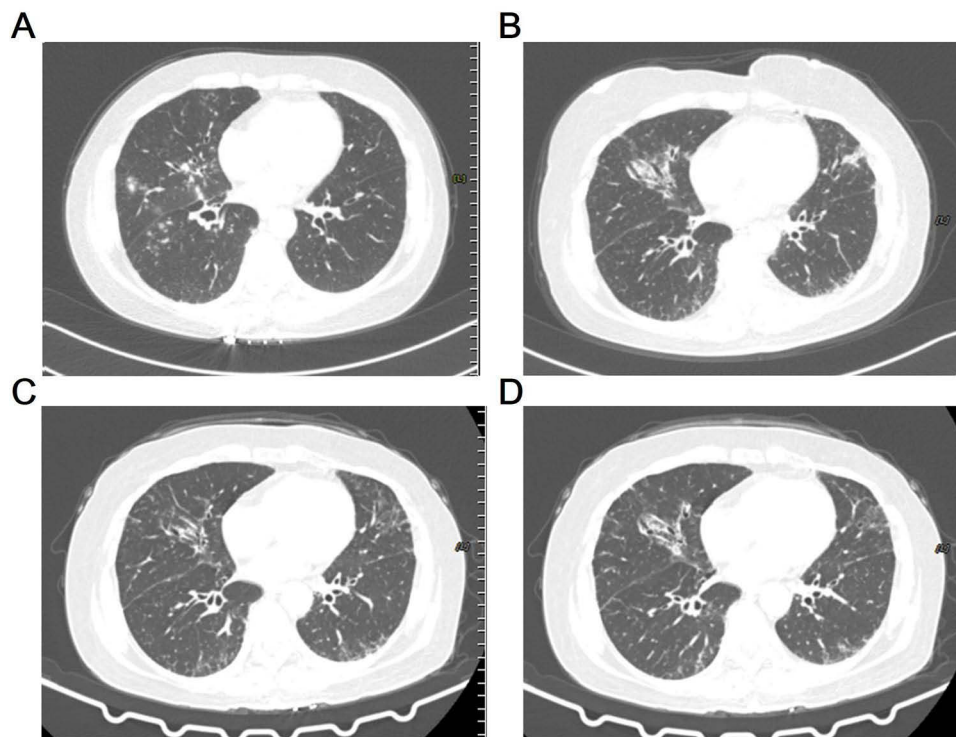


Figure 1 The chest CT pulmonary imaging of Case I. (A) On October 30, 2022, lung CT showed widespread small patchy spots in both lungs, particularly prominent in the basal segments of the lower lobes of both lungs and the middle lobe of the right lung, with local bronchial dilatation; (B) On March 25, 2024, lung CT showed scattered patches, nodules, and strip-like shadows in both lungs, with mild dilation of some bronchi; (C) On June 20, 2024, lung CT showed the *M. abscessus* lesion in the middle lobe of the right lung has absorbed; (D) On June 20, 2024, lung CT showed the aspergilliosis lesion has absorbed more than before.

Table 1 Summary of Results from Traditional Tests, mNGS and MALDI-TOF MS

| Patient | Submission Date | Sample | Traditional Microbiological Testing Results | mNGS Results | | | | Maldi-Tof Ms Results |
|---------|-----------------|-------------------------|---|--|-----------------|---------------|-----------------|----------------------|
| | | | | Strain | Gene | Mutation Site | Sequence Number | |
| Case 1 | 2022/11/04 | Sputum | Negative | MAB | <i>erm (41)</i> | T28 | 5209 | MAB, MAO |
| | | BALF | Negative | MAB | <i>erm (41)</i> | T28 | 5209 | |
| Case2 | 2023/03/14 | Sputum | | | | | | |
| | 2024/03/30 | BALF | <i>Aspergillus flavus</i> | <i>Aspergillus fumigatus</i> | | | 466 | |
| | 2023/10/07 | BALF | Negative | <i>M. abscessus</i> ; <i>Aspergillus flavus</i> | | | 20,702;6 | |
| | 2024/06/06 | Thoracic drainage fluid | <i>M. abscessus</i> | | | | | |
| | 2024/10/14 | Thoracic drainage fluid | NTM | | | | | |

Abbreviations: mNGS, Next-generation metagenomic sequencing; MALDI-TOF MS, Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; BALF, Bronchoalveolar lavage fluid; *M. abscessus*, *Mycobacterium abscessus*; MAB, *Mycobacterium abscessus* subspecies *abscessus*; MAO, *Mycobacterium abscessus* subspecies *bolletii*; NTM, *Nontuberculous mycobacteria*.

pandemic. Four months later, the patient visited another hospital, where auscultation revealed wet rales in both lungs. Her white blood cell count was 5.58×10^9 cells/L (reference range: 3.5–9.5), C-reactive protein (CRP) was 18.60 mg/L (0–8.2), Procalcitonin (PCT) was 0.059 ug/L (<0.064), FEV1/FVC was 76.08%. Liver and kidney function tests, Serum (1-3)- β -D-glucan test (G test, to detect fungal infections); Galactomannan Test (GM test, to assess invasive aspergillosis), and tumor markers CA125/CA153/CA724 showed no significant abnormalities. DNA of *Mycobacterium* in the sputum, tuberculosis X-pert, and tuberculosis RNA tests were negative. Acid-fast bacilli smear of sputum was positive. The Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) test on the sputum indicates that MAB and MMA are present.

The diagnosis of *M. abscessus* lung disease was confirmed. On April 19, 2023, the drug therapy started. In the initial phase, the patient experienced thrombocytopenia from linezolid and an allergic reaction to cefoxitin. Consequently, the final treatment regimen included intravenous (IV) amikacin and imipenem-cilastatin, along with oral moxifloxacin, minocycline, and clarithromycin. During the maintenance phase, the patient continued oral moxifloxacin, minocycline, and clarithromycin. On September 12, 2023, sputum mycobacterial culture converted to negative. On March 25, 2024, the patient experienced a recurrence of cough and sputum production after catching a cold, accompanied by wheezing. Auscultation revealed scattered moist rales in both lungs. Chest CT showed scattered patches, nodules, and strip-like shadows in both lungs, with mild dilation of some bronchi (Figure 1B). mNGS of BALF indicated *Aspergillus fumigatus*. Microscopic examination revealed a small number of white blood cells and *Aspergillus*-like hyphae. *Mycobacterium tuberculosis* DNA and acid-fast staining of sputum were negative. CRP was 14.92 mg/L (reference range: 0–8.2). White blood cells were 8.73×10^9 cells/L (reference range: 3.5–9.5). PCT, and liver and kidney function tests showed no abnormalities. The diagnosis of invasive pulmonary aspergillosis was confirmed. Clarithromycin was discontinued, and oral isavuconazole sulfate capsules were added for more than two months of treatment. A follow-up chest CT showed that the *M. abscessus* lesions were completely absorbed (Figure 1C), and the aspergillosis lesions looked better than before (Figure 1D). On July 7, 2024, the patient had no cough, sputum, or wheezing. Isavuconazole was discontinued. On September 24, 2024, FEV1/FVC was 78.86%. Laboratory indicators showed CRP 7.15 mg/L (0–8.2), white blood cells 8.73×10^9 cells/L (reference range: 3.5–9.5), TBIL 7.13 μ mol/L (3.4–17.1), ALT 15 U/L (5–40), AST 18 U/L (8–40), and serum creatinine 49 μ mol/L (59–104). Minocycline and moxifloxacin were also discontinued. The patient was monitored for four months after recovery with no recurrence. The detailed therapeutic course of Case 1 is illustrated in Figure 2.

Case 2

A 54-year-old male patient had recurrent blood-streaked sputum over the past year. On October 7, 2023, he was admitted to the hospital due to massive hemoptysis. He had lost 15 kg in weight in the past year. He had a history of emphysema and pulmonary tuberculosis for over 30 years, with the previous tuberculosis having been cured. Chest CT showed

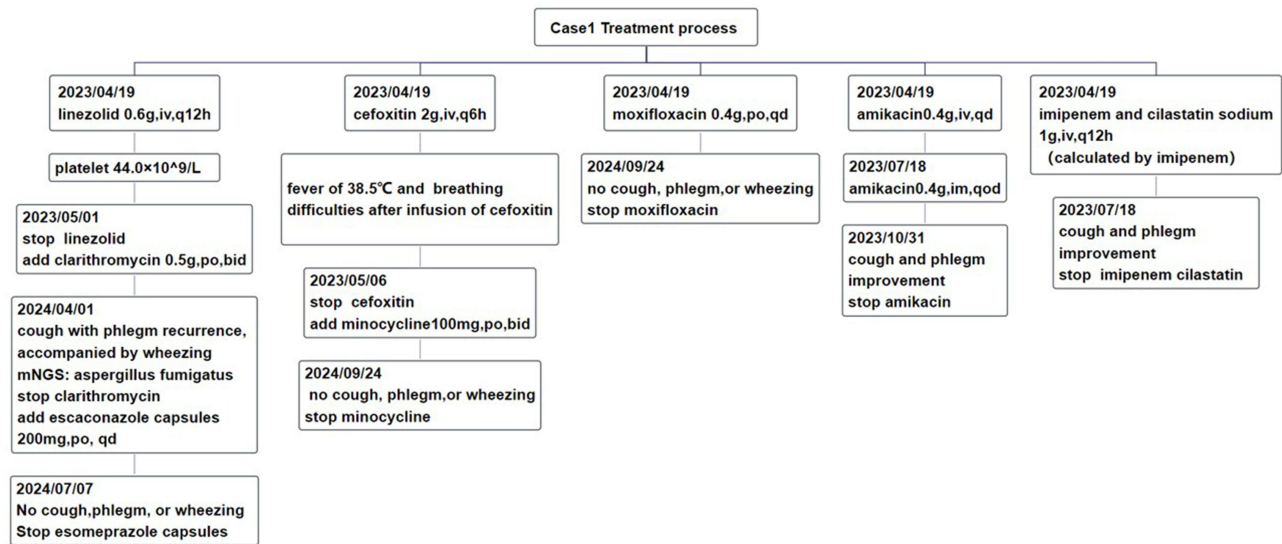


Figure 2 The treatment process of Case 1.

bilateral emphysema, bilateral lung infection, possible cavity formation in the upper lobe of the right lung, accompanied by partial bronchial dilatation (Figure 3A). Laboratory test white blood cell count was 14.62×10^9 cells/L (reference range: 3.5–9.5), CRP was 186.6 mg/L (reference range: 0–8.2), PCT was 0.285 µg/L (reference range: <0.064), and liver and kidney functions were normal. mNGS of BALF showed *M. abscessus* and *Aspergillus flavus* (Table 1). He expressed a reluctance to participate in strain identification and drug susceptibility testing. On October 12, 2023, thoracoscopic resection of the upper lobe of the right lung was performed, followed by the placement of a drainage tube. Lung tissue pathology revealed purulent lesions in the right lung, accompanied by microabscess formation and chronic granulomatous inflammation.

He was diagnosed with *M. abscessus* lung disease. After surgery, he was started on IV imipenem cilastatin sodium, linezolid, and amikacin, combined with oral moxifloxacin therapy. The patient has no hemoptysis. His white blood cell count was 9.67×10^9 cells/L (reference range: 3.5–9.5), CRP was 19.87 mg/L (0–8.2), and liver and kidney functions show no abnormalities. He was requested to continue treatment at the local hospital. The local hospital did not follow the recommended medical advice but instead administered oral anti-tuberculosis treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol for four months. His cough, phlegm, and shortness of breath did not improve, and the drainage tube continued to discharge yellowish-green fluid daily. Chest CT scan on February 27, 2024, showed absence of the upper lobe of the right lung, accompanied by cavity shadows and air-fluid levels. Lesions in the middle lobe of the right lung increased, and segmental atelectasis and bronchiectasis appeared in the posterior segment of the upper lobe of the left lung, with exacerbated



Figure 3 The chest CT pulmonary imaging of Case 2. (A) On October 11, 2023, Lung CT showed Cavity in the right upper lobe, accompanied by bronchiectasis; (B) On February 27, 2024, Lung CT showed the right upper lobe is missing, with cavitory shadows and air-fluid levels, and the lesions in the right middle lobe have increased.

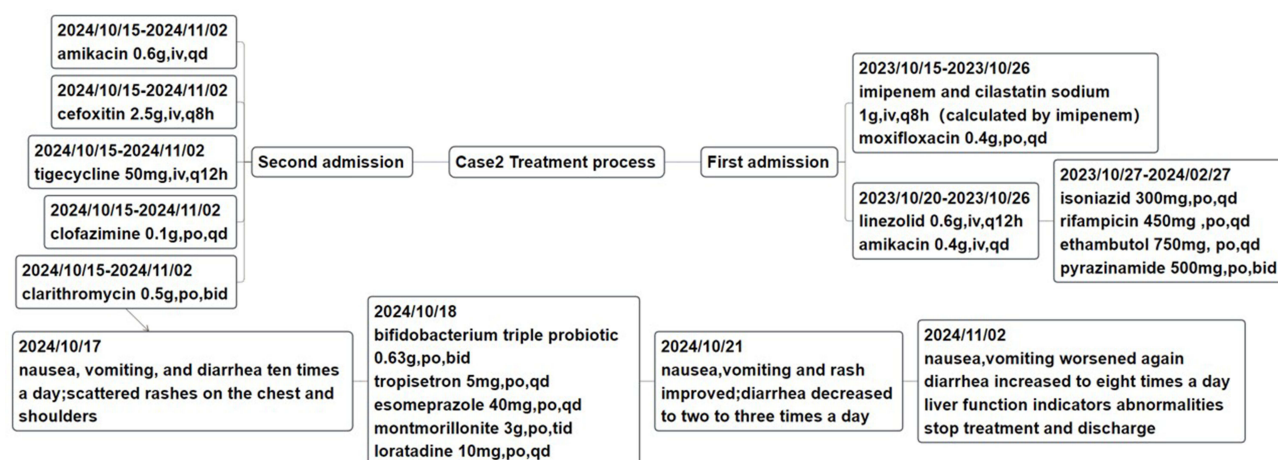


Figure 4 The treatment process of Case 2.

emphysema in both lungs (Figure 3B). After discontinuing anti-tuberculosis drugs. He went to several hospitals to get checked, but they did not give him any treatment. On June 6, 2024, an outpatient NTM culture (thoracic drainage fluid) revealed a small amount of *M. abscessus*. Antimicrobial susceptibility test (cultured for 12 d): amikacin is sensitive, cefoxitin (MIC 64 µg/L) and clarithromycin (MIC 4 µg/L) are moderately sensitive, the rest are resistant. But he refused hospitalization and planned to take the test report back to our hospital for continued treatment. On October 13, 2024, he was readmitted to our hospital. Laboratory tests showed white blood cell count of 8.94×10^9 cells/L (reference range: 3.5–9.5), CRP of 67.22 mg/L (reference range: 0–8.2), total bilirubin (TBIL) of 23.08 µmol/L (reference range: 3.4–17.1), alanine aminotransferase (ALT) of 19 U/L (reference range: 5–40), aspartate aminotransferase (AST) of 21 U/L (reference range: 8–40), alkaline phosphatase (ALP) 47 U/L (reference range: 45–125 U/L), and serum creatinine of 52.4 µmol/L (reference range: 59–104). The culture of thoracic drainage fluid for NTM shows a positive result in small amounts. The treatment plan includes iv amikacin, tigecycline, and cefoxitin, along with oral clarithromycin and clofazimine for combination therapy. Two days later, the patient developed nausea, vomiting, and diarrhea ten times a day, along with scattered rashes on the chest and shoulders. After symptomatic treatment, nausea, vomiting and rash improved, and diarrhea decreased to two to three times a day. On November 2, 2024, nausea, vomiting, and diarrhea have worsened again, with diarrhea increasing to 8 times a day. Laboratory tests showed white blood cell count of 7.43×10^9 cells/L (reference range: 3.5–9.5), CRP of 69.04 mg/L (reference range: 0–8.2), TBIL of 40.54 µmol/L, ALT at 65 U/L, and AST at 63 U/L, and ALP at 358U/L. The patient requested to stop treatment and be discharged. Unfortunately, he passed away one month later. The detailed therapeutic course of Case 2 is illustrated in Figure 4.

Diagnosis

The diagnosis of NTM disease should be based on a comprehensive assessment of microbiological, clinical, imaging, and pathological examination results.

Microorganisms

In recent years, *M. abscessus* lung disease has gradually become a clinically frequent disease. The increase in incidence can be attributed not only to increased environmental exposure, an aging population, and a rise in chronic lung disease but also to advancements in microbiological diagnostic techniques. With the development of molecular biology technologies, mNGS and MALDI-TOF MS have been widely used in the diagnosis and treatment of NTM lung disease due to its higher sensitivity, faster sequencing speed.^{3,15,20} Guidelines recommend that a single positive culture of NTM from bronchial washings or bronchoalveolar lavage fluid and/or molecular biological testing is sufficient;⁹ however, this standard may be somewhat rough in cases with very few sequences, potentially leading to misdiagnosis or overdiagnosis.⁹ It is suggested that both NTM culture and molecular biological detection of bronchial washings or bronchoalveolar lavage fluid should be positive simultaneously. Case 2 utilized

traditional microbial culture combined with mNGS to discover the pathogenic bacteria *M. abscessus*, while Case 1 employed mNGS and MS to identify the pathogenic MAB and MAO. Modern molecular biology techniques provide a basis for precise diagnosis in pathogen identification.

Imaging and Clinical Symptoms

The guidelines recommend that individuals with respiratory symptoms and/or systemic symptoms, who show cavitary shadows, multifocal bronchiectasis, and multiple small nodular lesions on chest imaging, and meet the criteria for microbiological evidence while excluding other pulmonary diseases, can be diagnosed with NTM lung disease.⁹ Case 1 showed bronchiectasis on chest CT, with symptoms of cough and phlegm. Case 2 exhibited fibrous cavities on chest CT, with symptoms of hemoptysis, while excluding other diseases such as pulmonary tuberculosis and lung cancer. The clinical manifestations and imaging features of these two patients are consistent with the guidelines.

Pathology

The lung tissue biopsy in Case 2 revealed granulomatous inflammation, which is a histopathological characteristic change of mycobacteriosis.

Based on the clinical manifestations, etiology, imaging, and pathological results of both cases, the diagnosis of *M. abscessus* lung disease is confirmed.

Treatment

Drug treatment and Adverse Reaction Monitoring of *M. abscessus* Lung Disease

Drug treatment

M. abscessus demonstrates formidable multidrug resistance characterized by three distinct patterns: intrinsic (constitutive) resistance, acquired resistance, and inducible resistance.²¹ The intrinsic resistance primarily stems from its low-permeability cell wall²² (composed of peptidoglycan, arabinogalactan, and long-chain mycolic acids) and efflux systems.²³ High-expression efflux pumps such as MmpL and Tap in the outer membrane substantially reduce intracellular antibiotic concentrations through active efflux mechanisms. Specifically, the MmpL efflux pump mediates cross-resistance between clofazimine and bedaquiline,²⁴ while the Tap pump contributes to amikacin resistance.²⁵ Efflux pump inhibitors including thioridazine, verapamil, and MmpL3 inhibitors may enhance antibiotic efficacy through efflux inhibition or cellular metabolic interference, presenting promising therapeutic strategies.^{21,23} Acquired resistance typically arises from genetic mutations (eg, in *rrl* (23S rRNA)²⁶ and *rrs* (16S rRNA)²⁷ and production of β -lactamase (BlaMab),²⁸ conferring resistance to macrolides, aminoglycosides, and β -lactams. β -lactamase inhibitors such as avibactam,²⁸ vaborbactam,²⁹ durlobactam³⁰ and relebactam³¹ can suppress BlaMab activity and potentiate β -lactam antibiotics (eg, meropenem, ceftaroline, sulopenem, imipenem-cilastatin and ceftazidime),^{28,29,31} though clinical validation remains pending. Inducible resistance is particularly prevalent with macrolides, associated with thymine at position 28 of the *erm* (41) gene (T28 genotype).^{32,33} Therefore, *erm* (41), *rrl*, and *rrs* gene testing are strongly recommended when administering macrolides or aminoglycosides.

In Case 1, the genetic characterization of *M. abscessus* revealed the *erm* (41) T28 genotype. In Case 2, while *M. abscessus* was cultured pre- and post-operatively, the absence of species identification and genetic testing precluded differentiation between persistent infection and disease recurrence. And there is currently study indicates that regardless of whether it is a recurrence or reinfection, the treatment plan remains the same as the initial treatment, depending on the susceptibility of the isolated strain to macrolide antibiotics.³⁴ According to CLSI standards, the minimum inhibitory concentration (MIC) for macrolide-sensitive strains should be ≤ 2 μ g/mL, but the MIC of this strain for clarithromycin is 4 μ g/mL. Meanwhile, most isolates of MAB and MAO have active *erm* genes, which make them resistant to macrolides.³⁵ However, almost all isolates of the MMA do not have active *erm* genes and are sensitive to macrolides. Based on this, we speculate that the cases of 1 and 2 may have been infected with MAB and/or MAO with active *erm* genes, and therefore both adopted treatment regimens targeting inducible macrolide-resistant *M. abscessus*.

Clinical guidelines and study suggested that for patients with infection-induced macrolide-resistant *M. abscessus*, the initial treatment regimen should include at least four combined drugs, including a macrolide and amikacin.^{9,36,37} Other optional drugs include imipenem/cilastatin, cefoxitin, tigecycline, clofazimine, and linezolid. The duration of this phase should be at least a month, with a recommendation to extend it to 3 to 6 months. The maintenance phase should include at least three orally active drugs, such as linezolid, minocycline, ciprofloxacin, moxifloxacin, rifabutin, or clofazimine, or the option of nebulized amikacin. The treatment should continue until the sputum culture results are negative and should be maintained for at least one year. Case 1 ultimately chose amikacin, imipenem and cilastatin sodium, moxifloxacin, minocycline, and clarithromycin for treatment for over 6 months in the initial phase, and in the maintenance phase, moxifloxacin, minocycline, and clarithromycin were used for 5 months, followed by moxifloxacin and minocycline for over 5 months. The treatment was ultimately successful, with no recurrence during the 4-month follow-up. Case 2 restarted treatment one year after surgery. In the initial phase, the patient was treated with amikacin, cefoxitin, tigecycline, clofazimine, and clarithromycin. However, treatment was discontinued due to intolerance from adverse drug reactions. Unfortunately, the patient passed away a month after discharge.

Both Case 1 and Case 2 included clarithromycin and amikacin in their treatment regimens. Clarithromycin is a macrolide antibiotic. However, it is not considered an effective antibacterial agent in this context, but rather as an immunomodulator,³⁸ inhibiting inflammatory factors, reactive oxygen species (ROS), the formation of neutrophil extracellular traps, and leukotriene synthesis, thereby enhancing bactericidal effects. And some studies have shown that clarithromycin used in a multi-drug combination regimen for patients with macrolide-resistant infections has achieved good therapeutic outcomes,^{39,40} consistent with the results of Case 1. Amikacin is currently considered the second most important drug for treating *M. abscessus*,^{10,36} and its resistance is clearly correlated with the efficacy of treatment for mycobacteriosis. In addition, amikacin is usually sensitive and can significantly improve treatment success rates when combined with other antibiotics such as imipenem, cefoxitin, clarithromycin, ciprofloxacin, and linezolid.^{37,41} Furthermore, the inhaled formulation of amikacin (ALIS) has shown promising prospects in the treatment of drug-resistant *M. abscessus* infections, enhancing drug concentration at the site of infection while reducing systemic toxicity, providing a new treatment approach.⁴² Due to drug availability, we did not select ALIS for the maintenance phase.

Apart from the two core drugs, macrolides and amikacin, there is currently no standard combination regimen. There is currently evidence indicate that the combination of two β -lactam antibiotics (cefoxitin/imipenem, ceftolozane/imipenem, and ceftazidime/ceftolozane) can better inhibit D, D-transpeptidase,⁴³ thereby inhibiting the synthesis of the mycobacterial cell wall, which is beneficial for killing NTM and provides a new direction for future treatments. However, our patient was initially treated with imipenem-cilastatin combined with cefoxitin.

Moxifloxacin shows relatively weak antibacterial activity against *M. abscessus* and is mainly used for maintenance therapy or as an alternative treatment in cases of drug allergy. Minocycline is a tetracycline drug, with tigecycline and doxycycline being its counterparts. Weihe Zhang found extremely high resistance rates of *M. abscessus* to doxycycline and minocycline in vitro, at 93% and 87.2%, respectively, but increased susceptibility to tigecycline with a resistance rate of only 7.2%.⁴⁴ YongSoo Kwon also found that treatment regimens containing tigecycline showed significant improvements in symptoms and imaging results in *M. abscessus* lung disease, but the rate of microbiological improvement was poor, and adverse reactions were common.⁴⁵ Therefore, caution is advised when selecting tigecycline for treatment. In Case 1, we chose a combination regimen of minocycline during the maintenance treatment phase, which showed good efficacy, but its effectiveness was inconsistent with the literature reports.⁴¹ On the other hand, in Case 2, we selected a combination regimen of tigecycline during the initial phase, resulting in intolerable adverse reactions, which were consistent with the safety reported.⁴¹

Monitoring of Adverse Drug Reactions

Due to the numerous types and quantities of medications for treating *M. abscessus* lung disease, as well as the long duration of treatment, nearly 80% of patients experience adverse reactions during treatment.⁴⁶ Therefore, monitoring of adverse drug reactions is particularly important.

In the Case 1, the patient experienced thrombocytopenia from linezolid and an allergic reaction from cefoxitin while on medication. Tedizolid, a novel oxazolidinone antibiotic, might be a good alternative to linezolid.⁴⁷ It has advantages in terms of antibacterial activity, side effects, and drug interactions. However, our patient did not choose tedizolid due to price and drug accessibility issues. After 18 d of using cefoxitin, the patient developed a fever and respiratory distress that were unbearable, leading to stopping the medication. This is consistent with reports stating that cefoxitin has poor

tolerability, with an average use of only 22 d.⁴⁸ However, the regimen also contained imipenem, which is also a β -lactam medication. We could not determine whether imipenem was involved in the allergic reaction, but we still caution that the risk of adverse reactions may increase when similar drugs are used in combination, and close monitoring is required.

In Case 2, the patient developed gastrointestinal symptoms, including diarrhea, vomiting, and nausea, accompanied by liver injury. YongSoo Kwon reported that tigecycline, cefoxitin, amikacin, clarithromycin, and clofazimine can all cause gastrointestinal reactions such as nausea, vomiting, and diarrhea, but tigecycline has the highest incidence rate, reaching 85%–94.2%.⁴⁹ Even after using antiemetic medications like ondansetron to help with tigecycline tolerance, gastrointestinal reactions still occurred at a rate of 77.1%, resulting in a 57.1% rate of stopping or reducing the dosage.^{45,50} Our patient initially showed improvement in diarrhea and vomiting symptoms after using tropisetron hydrochloride tablets, esomeprazole enteric-coated capsules, and bifidobacterium triple viable capsules. However, as the treatment duration extended, the improvement in symptoms was not significant, which is consistent with the above literature reports.^{45,50} Clarithromycin, clofazimine, and tigecycline can all cause liver injury. Clarithromycin can cause mild asymptomatic elevations in serum alanine aminotransferase (ALT) levels in about 1–2% of the population⁴⁸ and can also lead to acute liver failure,⁵¹ especially when used concurrently with certain hepatotoxic antibiotics, which can exacerbate clarithromycin-induced liver injury.^{48,51} Tigecycline-induced liver injury is characterized by elevated serum ALT/AST and bilirubin levels, as well as hepatic failure.⁵² This is especially common in patients with high maintenance doses (200 mg/d), long treatment durations (more than 14 d), and the use of multiple hepatotoxic drugs, with an incidence rate as high as 5%–10.3%.^{50,53,54} Clofazimine itself is not associated with elevated serum aminotransferase levels or clinically significant acute liver injury during treatment, but its combined use with other hepatotoxic drugs such as clarithromycin and tigecycline can increase the risk of hepatotoxicity.^{55,56} Therefore, we conclude that the gastrointestinal reactions and liver damage in this patient are likely caused by the combined effects of several drugs.

In summary, when deciding on treatment for *M. abscessus* lung disease, clinicians must comprehensively consider multiple factors such as the type of NTM subspecies, the severity of the disease, the drug of sensitivity, pharmacokinetics/pharmacodynamics (PK/PD) characteristics, adverse reactions and interactions, patient tolerability, treatment costs, drug accessibility, etc. They should weigh the pros and cons and make comprehensive judgments.

Surgical Treatment

Surgical treatment has demonstrated significant effectiveness in the management of many diseases, especially in dealing with complex cases. Lung resection can serve as an adjuvant therapy for drug in specific patients with *M. abscessus* lung disease. Such patients should meet the following criteria: good cardiopulmonary function, able to tolerate surgery, with localized or isolated lesions, and with poor response to medical treatment or complications requiring surgical intervention, such as hemoptysis.^{9,57,58} Surgical options include segmentectomy, lobectomy, and pneumonectomy. After lung resection surgery, 99.5% of patients had negative sputum results, while 8.2% experienced microbial recurrence.⁵⁹ Therefore, it is recommended to continue anti-NTM treatment until sputum culture results are continuously negative for at least one year. Surgical options include segmentectomy, lobectomy, and pneumonectomy. After lung resection surgery, it is still recommended to provide NTM treatment until the sputum culture results remain negative for more than a year.^{57,58} In Case 2, the patient had massive hemoptysis, which met the surgical indications. However, after the surgery, the patient did not get timely drug sensitivity testing or continue treatment for the mycobacterial infection as advised by the doctor, which led to the condition getting worse. One year later, a five-drug combination therapy including clarithromycin was chosen based on the drug sensitivity results, but the treatment still did not work. Therefore, although lung resection can effectively remove the lesion, it cannot completely guarantee the elimination of potential sources of infection in the body in patients with complex conditions, and surgical treatment should still be approached with caution.⁶⁰ Postoperative combination with sensitive drug therapy is very necessary, and the duration of drug use should be based on the patient's overall health, the extent of the infection, the type of surgery, the doctor's skill level, how well the lesions were cleared, and how the patient is recovering.

Follow-Up Management

Management of Recurrence

A recurrence of NTM is a second episode of NTM occurring after a first episode had been considered cured. In particular, patients with a longer interval between initial diagnosis and treatment, multiple lung lobes affected, and failure to convert to negative sputum culture within 6 months after the initiation of treatment, as well as those with nodular bronchiectatic type, have a higher recurrence rate,⁶¹ ranging from 9–33%.^{62,63} Recurrence mainly occurs within one year after cure.⁶⁴ Most recurrences are attributed to reinfection with new genotypes rather than recurrent infection with not the same strain. And data indicates that 78% of recurrences after the clearance of *M. abscessus* are caused by reinfection with different strains.⁶³ Case 1 is about a bronchiectasis patient who did not get timely treatment after their initial diagnosis and has high recurrent risk factors. Four months after the initial diagnosis, the patient experienced reinfection with MAO. After treatment, there was no relapse in the 4 months following treatment, but they need close monitoring, and it is a good idea to do sputum mycobacterial cultures every 6 months.

Management of Complications

Patients with NTM lung disease often exhibit abnormal host defense functions and immunodeficiency. Additionally, their lung tissue structure is often damaged, accompanied by airflow obstruction. These factors create a favorable environment for fungal survival, making it easy to lead to secondary or concurrent *Aspergillus* infections.^{16,65} According to the onset time, Case 1 detected *Aspergillus* at the time of NTM lung disease diagnosis, while Case 2 was discovered 1.4 years later, and both findings occurred earlier than the 1.5–7 years reported in the literature.¹⁸ When two diseases coexist, the imaging usually presents as thickening of the lung cavity, surrounding infiltration, and fungal ball or aspergilloma. However, the imaging findings of Case 1 show interstitial changes in both lungs, which are inconsistent with the descriptions in the literature.⁶⁵ In the treatment, the clinical improvement of patients is more related to the response to antifungal therapy, suggesting that antifungal treatment should be prioritized before treating NTM to avoid unnecessary interactions. In Case 1, to avoid delaying the condition, we added the antifungal agent voriconazole and discontinued clarithromycin. In Case 2, the sequence count of *Aspergillus* is relatively low, and we do not consider it a pathogenic organism at this time. Instead, we will enhance the monitoring of sputum fungal smears and cultures, serum G and GM tests, and *Aspergillus* IgG antibodies. Once *Aspergillus* infection is detected, azithromycin, which has less interaction with voriconazole, can be chosen as a substitute for clarithromycin.⁶⁶

Preventive Measures

Environmental Control

Reducing exposure to NTM can decrease the risk of primary infection and recurrence after treatment.⁶¹ Therefore, high-risk individuals should minimize exposure to environments that may contain NTM, such as house dust, acidic and damp soil, water supply systems^{13,67–69} like showerheads, sink faucets, underground water pipes, indoor swimming pools, hot tubs, continuous positive airway pressure machines, humidifiers, and medicated bathtubs.¹⁵ Additionally, ventilation and disinfection should be enhanced.

Monitoring of High-Risk Populations

Early monitoring of high-risk populations is a key strategy for preventing NTM infections. In addition, the chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, pneumoconiosis, pulmonary tuberculosis, alveolar proteinosis, gastroesophageal reflux, cystic fibrosis genotypes, and abnormal alpha-1 antitrypsin phenotypes can all predispose individuals to NTM disease,^{3,15,65,70,71} especially among patients with post-tuberculosis bronchiectasis and fibrotic cavity diseases, where NTM infections are more prominent.⁷² Therefore, screening for NTM should be strengthened among these populations to promptly identify NTM lung disease. For patients diagnosed with NTM lung disease, they should receive timely treatment with sensitive antibiotics in a sufficient variety, adequate dosage, and for the appropriate duration to prevent complications.

Strategies for Enhancing the Immune System

After an infection occurs, host factors seem to be key determinants of progression. Therefore, enhancing the body's immunity is crucial. First, the use of medications that affect immunity should be minimized. Since tumor necrosis factor- α (TNF- α) is protective in NTM infections, which means TNF- α inhibitors like infliximab, etanercept, and adalimumab should be used less frequently.^{15,73,74} Drugs that affect immunity also include hormones, proton pump inhibitors, methotrexate.^{15,72}

Secondly, reasonable nutrition, appropriate exercise, rehabilitation training, and good living habits can significantly improve an individual's immune system.⁷⁵ Furthermore, immune intervention measures for specific populations, such as vaccination and the use of immunomodulators, may also play a positive role in preventing NTM infections.

Patient Education and Self-Management

Patient education and self-management are important components in preventing NTM infections.^{76,77} It is essential to actively carry out a series of health science training with the theme of "NTM lung disease cognition-prevention-treatment-rehabilitation" to help patients master self-management methods, thereby enhancing their understanding and coping abilities towards the disease.

Conclusion and Prospect

Through clinical practice in *M. abscessus* lung disease, this article found that molecular biology technology mNGS has significant diagnostic value in species identification of NTM lung disease and detection of drug-resistance genes. Early initiation of standardized antimicrobial therapy upon diagnosis is crucial to prevent reinfection and disease progression. The treatment protocol should closely monitor adverse drug reactions, with routine tests including complete blood count, kidney function (urea nitrogen, creatinine), liver enzymes, and gastrointestinal symptoms (nausea, diarrhea); special drug monitoring includes aminoglycosides (vestibular function and hearing), chloramphenicol (skin and mucosal pigmentation), macrolides (hearing, QT interval), quinolones (photosensitivity, tendon damage), and β -lactams (allergic reactions). For complex cases, a combined treatment regimen of surgery and medication should be considered when necessary. Meanwhile, this article also emphasizes that follow-up management after the cure of NTM lung disease cannot be ignored.

By reviewing the literature, this article proposes further research directions for the diagnosis and treatment of *M. abscessus* lung disease. Future research should focus on new explorations of drug-resistance mechanisms and the discovery of new genes to promote the development of related fields. At the same time, efforts should be made to preserve the activity of existing antibacterial drugs, especially macrolide antibiotics and amikacin. Furthermore, the future work should also include the development of new therapeutic drugs, vaccines, natural products, or plant extracts, as well as the research and development of targeted agents for genes such as *erm* (41), *whiB7*, and *MmpL3*. Finally, the effectiveness of existing novel drugs (such as omadacycline, tedizolid, double β -lactam combinations, and bacteriophages) should be verified to address the challenges of NTM lung disease.

Consent for Publication

Written informed consent was obtained from the patient's family of the deceased patient or the patient himself for the publication of any data included in this work. The cases' details are open access and can be browsed without institutional approval.

Author Contributions

All authors made substantial contributions to the conception, study design, execution, acquisition of data, analysis, and interpretation; participated in drafting the manuscript or critically revising it for intellectual content; gave final approval of the version to be published; agreed to submit to the current journal; and take responsibility for all aspects of the work, ensuring integrity and accuracy.

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