Respiratory Medicine Case Reports 38 (2022) 101668

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Case studies to illustrate good practice in the management of non-tuberculous mycobacterial pulmonary disease

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ARTICLE INFO

Keywords:
Atypical mycobacteria
Non-tuberculous mycobacteria
Respiratory infection
Imaging
Case studies

ABSTRACT

Pulmonary disease caused by non-tuberculous mycobacteria (NTM-PD) can be a complex condition for health care providers to manage, and delayed diagnosis and treatment failure are common. Here we present three case studies that illustrate key challenges in the diagnosis and treatment of NTM-PD, and provide guidance on these issues. In addition, we make recommendations on how the overall management of NTM-PD may be improved, through strategies such as physician education to recognise NTM-PD, and the development of multidisciplinary teams and patient-support groups.

1. Introduction

Non-tuberculous mycobacteria (NTM) consist of all mycobacterial species except those causing tuberculosis and leprosy [1,2]. NTM are found ubiquitously in the environment and >190 species have been identified to date [3]. Although most are clinically insignificant, several species of NTM can cause pulmonary disease in humans (NTM-PD), which remains a challenging condition for healthcare providers to diagnose and manage [4]. Several risk factors for NTM-PD have been identified, including demographic characteristics, medical conditions, structural lung diseases, an abnormal immune response, and drug treatments [1,2,4,5] (Table 1).

Guidelines recommend NTM-PD should be diagnosed based on a combination of clinical, radiological, and microbiological findings [3,6] (Fig. 1). However, for several reasons, this is not always straightforward [5]. Firstly, its presentation and ongoing symptoms are non-specific, and may be obscured by pre-existing lung conditions such as bronchiectasis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). Secondly, NTM are ubiquitous in the environment and can transiently colonise the airways without causing disease [1,4]. Thirdly, chest X-rays may appear normal, near-normal or non-specifically abnormal [5] which can result in NTM-PD being missed or misdiagnosed (Fig. 2) [2,5]. More recently, a biomarker of NTM-PD (serum anti-glycopeptidolipid-core IgA) has been identified, which may aid in the diagnosis of NTM-PD [7].

Treatment of NTM-PD is also challenging and there is a lack of standardisation in treatment and management pathways due to a limited evidence base [4]. A typical treatment course involves use of several antibiotics for 1–2 years, which can be associated with significant adverse effects and drug-drug interactions [2,3,8]. Furthermore, treatment is often unsuccessful in curing NTM-PD [9].

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https://doi.org/10.1016/j.rmcr.2022.101668
Received 11 February 2022; Received in revised form 16 April 2022; Accepted 17 May 2022
Available online 23 May 2022

Table 1
Risk factors for NTM-PD.

Demographic characteristics	Medical conditions	Structural lung disease	Abnormal immune response	Immunosuppressive drugs
Increasing age	Gastro-oesophageal reflux disease	COPD	Diabetes	Biological therapies
Female sex		Bronchiectasis	Rheumatoid arthritis	Corticosteroids including inhaled treatment
Low BMI Alcohol misuse Smoking		Cystic fibrosis Pneumoconiosis	Chronic kidney disease	

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NTM-PD, pulmonary disease caused by non-tuberculous mycobacteria; TNF, tumour necrosis factor.

Therefore, a positive diagnosis of NTM-PD should not automatically lead to antibiotic treatment, particularly in patients with mild symptoms [1,3,4,6].

In this article we present three case studies of patients with NTM-PD, designed to illustrate the challenges facing clinicians and provide advice on best practice for its diagnosis and management.

2. Case studies

2.1. Case study 1

A 66-year-old female was referred to a general respiratory clinic with a 2-year history of worsening breathlessness and a dry cough. She reported that although she could walk comfortably on flat ground, she had to stop after 50 m on even a gentle incline. The patient had stopped smoking around 15 years earlier (with a 5 pack-year history), drank minimal alcohol, and had a body mass index (BMI) of 19 kg/m^2. There was a history of drug-controlled hypertension and poor peripheral circulation, for which she was also receiving treatment. She had required antibiotics more frequently than usual over the preceding 24 months, experienced continuous rhinitis, and had some gastrointestinal discomfort with marked gastro-oesophageal reflux disease (GERD). She also experienced occasional chest tightness that was not related to exercise and had a family history of ischemic heart disease. Chest X-rays in both primary care and the respiratory clinic were normal, and spirometry showed moderate obstructive airway disease (forced expiratory volume in 1 second [FEV1] = 68%; forced vital capacity [FVC] = 85%).

It was initially felt that the patient had a smoking-related lung disease such as COPD with possible reversibility, and she was treated with bronchodilators, inhaled corticosteroids, and then a trial of oral corticosteroids. However, none of these improved her symptoms, and the chest tightness and need for frequent antibiotics continued. The patient was referred to cardiology, where an electrocardiogram and *trans*-thoracic echocardiogram were reported as normal, and she was referred back to the respiratory clinic. After another 10 months of monitoring with no symptomatic improvement, the patient stopped attending clinic and was lost to follow-up.

Three years later, the patient was referred back to the respiratory clinic by her general practitioner due to a worsening productive cough. In addition, her exercise tolerance had decreased significantly, and she was now worried about leaving the house. A chest X-ray and high-resolution computed tomography (HRCT) scan were performed (Fig. 3A). The HRCT scan showed bronchiolitis and bronchiectasis throughout both lungs, predominantly in the upper lobes but with airway changes (including air trapping and small airways disease) also present in both lower lobes. Serial sputum cultures repeatedly isolated *M. intracellulare*. On review of her case notes it was

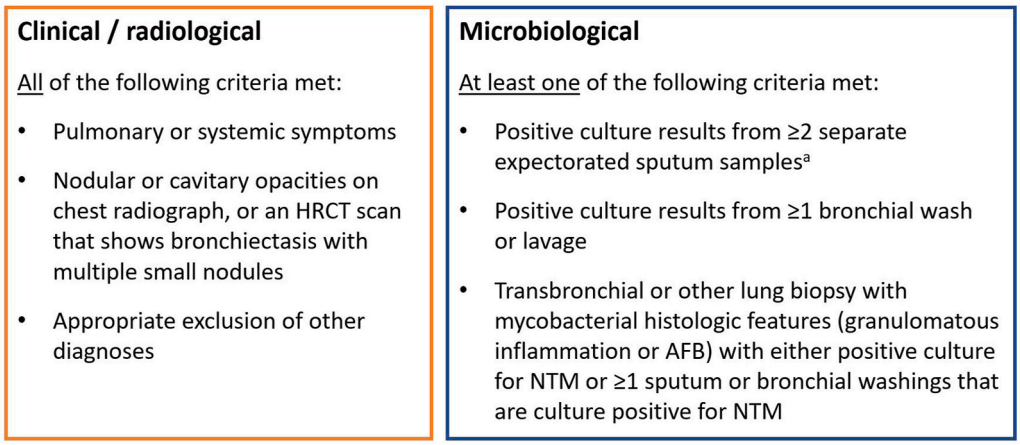

Fig. 1. Diagnostic criteria for NTM-PD (adapted from). Both the clinical/radiological and microbiological criteria must be met for a confirmed diagnosis of NTM-PD.
[a] If the results are non-diagnostic, consider repeat sputum AFB smears and cultures.
AFB, acid fast bacilli; HRCT, high-resolution computed tomography; NTM-PD, pulmonary disease caused by non-tuberculous mycobacteria.

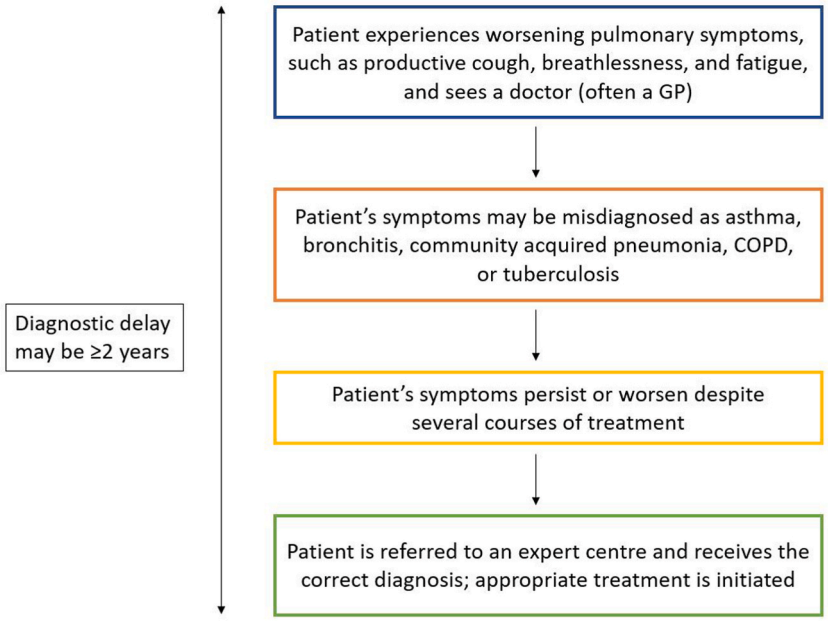

Fig. 2. A common patient journey in NTM-PD.
COPD, chronic obstructive pulmonary disease; GP, general practitioner; NTM-PD, pulmonary disease caused by non-tuberculous mycobacteria.

apparent that testing for NTM had not been performed during the previous assessment.

The patient was therefore referred to a specialist NTM team and the diagnosis of NTM-PD was confirmed based on presence of clinical symptoms, evidence of radiological change consistent with NTM-PD, and repeated positive sputum cultures for *M. intracellulare* (Fig. 1). Full lung function testing indicated apparently moderate airway obstruction on spirometry (FEV1 = 0.93 L [60% of predicted]; FVC = 1.76 L [92% of predicted]) but markedly reduced maximal expiratory flow (MEF) 75, 50 and 25 at 0.98 L (21% of predicted), 0.47 L (15% of predicted), and 0.11 L (13% of predicted) respectively, as well as reduced diffusion capacity for carbon monoxide (DLCO = 2.13; 35% of predicted) and carbon monoxide transfer coefficient (KCO = 0.74; 51% of predicted). These results explained the patient's breathlessness. Following discussion with the patient, she commenced treatment for macrolide-sensitive *M. intracellulare* infection (based on drug sensitivity testing, and using the three-drug combination of thrice weekly oral azithromycin, ethambutol and rifampicin plus chest physiotherapy to facilitate sputum clearance from potentially obstructed small airways) and symptomatic treatment of GERD.

She had a good initial improvement in her respiratory symptoms of cough and sputum, and her cultures were negative for NTM within 2 months of starting therapy. However, she had considerable adverse events associated with her medication. These were mainly nausea, poor appetite and increased frequency of loose stools; though also included drug-drug interactions between rifampicin and her other therapy (particularly the antihypertensive medication and calcium antagonists, which were prescribed to improve her peripheral circulation), necessitating her to change or alter the dose of her existing cardiovascular medication. Despite discontinuing rifampicin, and remaining on just azithromycin and ethambutol, she finally had to stop all treatment after 9 months. She had seen little improvement in her breathlessness, and although her other symptoms have partially returned along with occasional positive mycobacterial sputum cultures (macrolide-sensitive), she does not wish to have further drug treatment. Her use of physiotherapy to clear sputum is intermittent, though she exercises with a walk for 20–30 minutes each day at a reasonable pace.

2.1.1. Challenges and learnings

A key challenge in the diagnosis of NTM-PD is the non-specific presentation of symptoms [5]. In this case, the patient presented with breathlessness and a dry cough, symptoms that could be caused by several conditions. The initial chest X-rays were normal or near-normal; and in a former smoker with possible COPD, a CT of the chest would be indicated to further define the cause of her symptoms (including identifying emphysema). When the chest CT was performed (together with full lung function testing), she was noted to have small airways involvement, presumably due to a combination of local inflammation and sputum plugging, which would explain her presentation with breathlessness. Mycobacterial cultures were not performed during the initial assessment, and an important opportunity for correct diagnosis was therefore missed. Such delays in NTM-PD are common, with the median time to correct diagnosis being reported as long as 2 years [10] (Fig. 2), and some patients may never receive a correct diagnosis.

With hindsight, however, there were clues that the symptoms may have been caused by NTM-PD. The patient had several risk factors for NTM-PD (Table 1), including female sex, low BMI, GERD, a diagnosis of COPD (although this may have been a misdiagnosis), and bronchiectasis [2,4]. Furthermore, the patient had symptoms that had not resolved following treatment and an increasing need for antibiotics. Her NTM-PD may have been worsened by the use of inhaled steroids [1], although these anti-inflammatory agents can be needed in patients with bronchiectasis and an "asthma phenotype" [11]. A key learning point from this case is that physicians

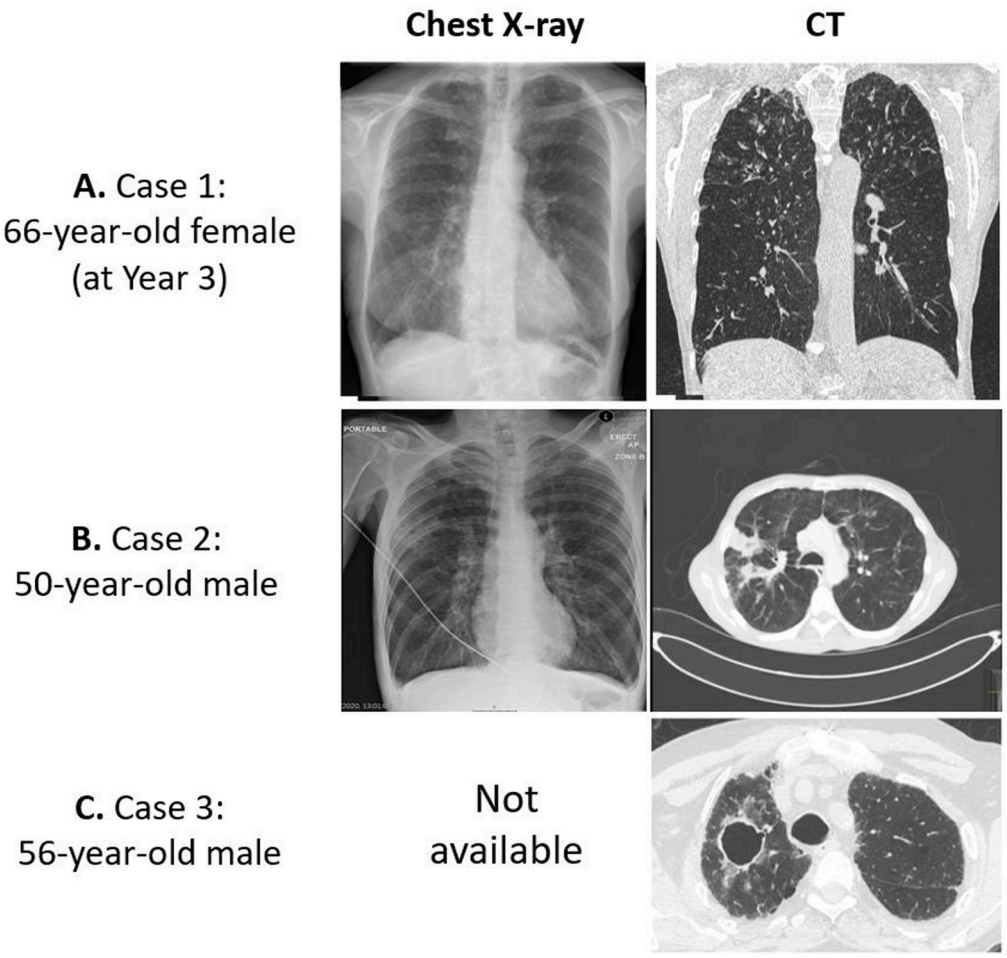

Fig. 3. Radiological results from the case studies of patients with NTM-PD.
CT, computed tomography; NTM-PD, pulmonary disease caused by non-tuberculous mycobacteria.

should have a high index of suspicion for NTM-PD in such patients, and send samples for microbiological analysis, as well as performing a CT scan as soon as possible.

This case also highlights the difficulties of treating NTM-PD. Long-term treatment with multiple antibiotics can cause significant side effects and drug-drug interactions, particularly as patients with NTM-PD are often elderly and may have multiple comorbidities [4,8]. In addition, the antibiotic regimens commonly used for NTM-PD are often not supported by rigorous clinical trials, relying instead on expert opinion or case series [3]. For example, whereas this patient was treated with thrice weekly oral azithromycin, ethambutol and rifampicin, the additional benefits of rifampicin in such a regimen are uncertain and currently being investigated [12]. Furthermore, it is unclear whether thrice-weekly or daily dosing of antibiotics is optimal, despite treatment guidelines recommending thrice-weekly treatment in non-severe *M. avium* complex (MAC) pulmonary disease [3,6].

It is therefore vital that treatment decisions are made jointly between the healthcare team and the patient, considering the patient's wishes and expectations for treatment as well as the risks and benefits [9,12]. In many cases, antibiotic treatment may not be appropriate, and management should instead focus on interventions such as chest physiotherapy and promoting a healthy body weight and good nutrition [4,12].

2.2. Case study 2

A 50-year-old male presented with a 2-month history of worsening breathlessness and a chronic productive cough. He also reported general malaise, weight loss, and night sweats, but no haemoptysis or chest pain. The patient was an active smoker (30+ pack years) with long-standing COPD and a history of crack cocaine use and alcohol misuse (although he stopped drinking 15 years ago). The patient was taking methadone 35 ml per day and inhaled steroids plus long-acting bronchodilator and anti-muscarinic agents once daily, and had no known drug allergies. He lived in sheltered accommodation and could only move with a mobility scooter.

On examination he was found to be cachectic and tachypnoeic at rest on air (88% O_2 saturation). He had a BMI of 14 kg/m^2, a respiratory rate of 20, and a pulse rate of 110 beats per minute. He had widespread respiratory wheeze, and no palpable lymphadenopathy. A chest X-ray showed right mid-zone consolidation with hyper-inflation and emphysema, in keeping with COPD and a

history of smoking and drug use (Fig. 3B).

The patient was admitted to hospital with Type 2 respiratory failure (tachypnoeic and oximetry: 85% in room air; arterial blood gas: pH 7.16, pO_2 6.9 kPa, pCO_2 10 kPa, HCO_3 31.6 mmol/L). He responded well to 2 L of oxygen via nasal cannula, nebulisers, steroids, and antibiotics, based on a diagnosis of community-acquired pneumonia. The patient had been symptomatic for the past two months with worsening productive cough. He tested negative for COVID-19 (both from a throat swab and a serology test), was HIV negative, and had no prior history of tuberculosis or contact with tuberculosis-infected individuals. However, sputum samples were sent for acid fast bacilli (AFB) testing; one smear sample was positive for AFB and two samples 9 days apart were culture positive for mycobacteria. A polymerase chain reaction (PCR) test was performed for *M. tuberculosis,* which was negative, suggesting potential infection with NTM. A sample was therefore sent for analysis by matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, which can rapidly speciate culture isolates, and this identified *M. avium*. This was subsequently confirmed by the reference laboratory through whole-genome sequencing and drug susceptibility testing showed no macrolide resistance.

Following the NTM-PD diagnosis, an HRCT scan was performed (Fig. 3B) and showed fibrocavitary disease. Based on this, and the smear-positive sputum sample, an initial 2 weeks of amikacin therapy plus the standard three drug regimen for *M. avium* infection (azithromycin, ethambutol and rifampicin) was started. Due to challenges with methadone administration, rifampicin was changed to clofazimine. At the time of writing, the patient is undergoing further tests for potential fungal infection ten months into NTM treatment, due to newly increased levels of *Aspergillus* antibodies, and he is being supported to stop smoking.

2.2.1. Challenges and learnings

This case again highlights the challenges of the non-specific symptoms associated with NTM-PD. The patient's presenting complaint of worsening breathlessness and a cough could have several causes, and as NTM-PD is relatively rare it can often take time to rule out other diagnoses, resulting in diagnostic delay (Fig. 2). However, the patient did have three risk factors for NTM-PD (COPD, low BMI and inhaled corticosteroid use; Table 1) and the case again illustrates the need for physicians to consider NTM-PD as a potential diagnosis and the importance of sending samples for microbiological analysis.

Another challenge highlighted by this case in the potential for co-infection with *Aspergillus* in patients with NTM-PD. In a recent single-centre study, over 60% of patients with NTM-PD had positive *Aspergillus* IgG and almost 40% had positive IgG and *Aspergillus* cultures [13]. Chronic pulmonary *Aspergillus* co-infection has been shown to be a strong predictor of mortality in patients with NTM-PD [14] and may complicate treatment due to the need for additional anti-fungal medications on top of the standard antibiotic regimens for NTM-PD. Moreover, rifampicin can complicate treatment of NTM where rifamycins necessitate larger doses of methadone; in this case the patient had severe withdrawal notwithstanding increased methadone dosing, and clofazimine was substituted for the rifamycin, with an increased frequency of electrocardiogram monitoring (to exclude lengthening QT interval on methadone, clofazimine plus a macrolide). This switch also gave the opportunity to commence antifungal azoles if required, although the risk of QT prolongation with azole therapy should be considered [15].

2.3. Case study 3

A 56-year-old male patient was referred by a local NTM service to a regional NTM clinic with a diagnosis of COPD, GERD and a history of being treated for NTM-PD for 12 months at a local hospital. The patient had developed worsening respiratory symptoms, which resulted in referral to an NTM clinic. He had an FEV1 of 50% predicted. Before starting treatment, he had a 6-month history of weight loss, occasional fevers (but not night sweats), and a cough. Sputum cultures at the other hospital had identified MAC (on two occasions) and *H. influenzae* and he was treated for two weeks with co-amoxiclav. This led to the sputum clearing of *H. influenzae*, but he remained culture positive for MAC and his symptoms did not improve. An HRCT scan before the start of treatment showed features consistent with NTM-PD, including cavities, nodules, and tree-in-bud changes.

The patient had been taking long-term azithromycin as prophylaxis for his COPD and the team at the local hospital started rifampicin, azithromycin, and ethambutol three-times weekly (without testing for macrolide susceptibility). However, after 12 months of treatment the symptoms had worsened, the patient now had large cavities with associated inflammatory changes, and sputum cultures were smear and culture positive for MAC.

Drug-susceptibility testing in the regional NTM clinic showed that the MAC was macrolide resistant. Consequently, and in view of the severe cavitary disease, intravenous amikacin was initiated, followed by nebulized amikacin (with careful monitoring for side effects) as per British Thoracic Society NTM-PD treatment guidelines. The patient also received oral rifampicin, ethambutol, linezolid, and clofazimine. Surgery, another potential option in these cases, was discussed with the patient, but was not performed as the antibiotic regimen led to improvement in the cavities and sputum culture conversion after 6 months. Treatment is ongoing, although it should be noted that the patient is unlikely to achieve eradication of disease with antibiotic therapy alone.

2.3.1. Challenges and learnings

This case highlights the challenges of treating NTM-PD, particularly problems caused by antibiotic resistance. Mycobacteria display intrinsic resistance to many antibiotics due to their thick lipid-rich cell wall and can develop additional mutational drug resistance [1, 8]. In particular, macrolide-resistant MAC, as was observed in this patient, is associated with limited treatment options and poor outcomes [16]. Testing for macrolide resistance in patients with NTM-PD prior to treatment is therefore critical. In addition, patients initiating long-term macrolide therapy for other conditions, such as COPD, should be screened for the presence of NTM [17] as there is a risk of inadvertently promoting macrolide resistance if NTM are present. However, many physicians fail to screen for NTM before initiating macrolide monotherapy, which greatly increases the risk that macrolide resistant NTM will develop [18].

Macrolide resistance in NTM can be either constitutive (due to a mutation in the 23S ribosomal RNA gene) or inducible (though the

expression of an erythromycin ribosomal methyltransferase gene [*erm*], which is seen in most *M. abscessus* isolates) [1]. Constitutive and inducible resistance should be tested for before initiating treatment, using either molecular techniques or prolonged (14-day) *in vitro* incubation with the drug [8,12].

3. Concluding remarks and recommendations

3.1. Patient issues

The three cases presented here illustrate many of the challenges associated with NTM-PD and show that improvements are needed in how the condition is diagnosed and managed. A common theme running through these case studies is diagnostic delay. This could be improved by educating healthcare teams in both primary and secondary care about the disease and its risk factors (Table 1), and the importance of sending samples for NTM testing and performing a CT scan, particularly in patients with risk factors who are not responding to standard therapy. These cases also highlight the challenges associated with treating NTM-PD, including lack of a strong evidence base for therapeutic decisions, adverse events associated with long-term antibiotic therapy, relatively low success rates with such treatments, and the impact of co-morbidities such as CF and COPD.

3.2. Organisation of care

One way that management of NTM-PD could be improved is the establishment of multi-disciplinary care teams. NTM-PD is a complex condition requiring a long duration of treatment ($\geq$12 months), and patients should be managed where possible by a specialist team including respiratory physicians, microbiologists, pharmacists, surgeons, radiologists, physiotherapists, nurses, dieticians and psychologists [4,6]. Such a team can ensure prompt diagnosis and optimal treatment, whilst also focussing on the holistic care of the patient. This can include managing adverse effects, improving treatment adherence, and providing support and advice, with the overall aim of maximising quality of life [4].

To support these multi-disciplinary teams, specialist centres could be created to provide advice and support to physicians managing complex cases of NTM-PD in their area and liaise with centres and units with specialist knowledge of related conditions such as CF or COPD. An example of a recent initiative in the UK is NTM Network UK (https://www.ntmnetworkuk.com/), which was created in response to the rising number of NTM infections identified in UK practice and aims to provide a framework in which NTM-PD can be systematically investigated, researched, and managed. Another important initiative is The European Bronchiectasis Registry (EMBARC; https://www.bronchiectasis.eu/), which is carrying out important research into NTM-PD.

The holistic model of patient care could also be enhanced by establishing patient support groups, which can provide information, support, and advice for patients living with this complex and long-term condition [12]. One such group is NTM Patient Care UK (https://www.ntmpatientcare.uk/), which was launched in 2018 and is the first patient association in the UK specifically for individuals with NTM. Its aim is to improve the lives of people with NTM infection in the UK by providing educational material and developing support networks, and allows patients with NTM-PD to interact and exchange information and advice.

Overall, these initiatives combined with the education of physicians and ongoing research should lead to improved outcomes for people living with NTM-PD.

4. Learning points

- Physicians should have a high index of suspicion for NTM-PD in patients with risk factors for the disease who fail to respond to standard treatment
- The decision to initiate antibiotic treatment for NTM-PD should be a shared decision with the patient, and the benefits and risks of treatment should be considered
- The creation of multi-disciplinary teams is essential to ensure optimal and holistic management of NTM-PD

Funding

Medical writing support was provided by MedicalGoGo (UK), which was funded by Insmed.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Simon Tiberi reports writing assistance was provided by Insmed Inc. Marc C. Lipman reports a relationship with NTM Patient Care UK that includes: board membership. Marc C. Lipman reports a relationship with NTM Network UK that includes: board membership. Marc C. Lipman reports a relationship with Insmed Inc that includes: consulting or advisory. Andreas Floto reports a relationship with Insmed Inc that includes: consulting or advisory and funding grants. Andreas Floto reports a relationship with Chiesi that includes: consulting or advisory and funding grants. Andreas Floto reports a relationship with GlaxoSmithKline Inc that includes: consulting or advisory and funding grants. Andreas Floto reports a relationship with AstraZeneca PLC that includes: consulting or advisory and funding grants.

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