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Case Series

NTM beyond the lungs: a case series of non-tuberculous mycobacterial infection at extrapulmonary sites

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ABSTRACT

Background: In this case series, the results of documented non-tuberculous mycobacteria (NTM) infections, which have emerged as important pathogens, mainly among individuals with immunocompromised status have been studied. The report showcases the clinical presentation, diagnostic modality, treatment as well as outcome and results regarding the 8 patients who were diagnosed with NTM infection at extrapulmonary locations via molecular techniques.
Methods: It involves retrospective analysis of patients who were diagnosed with NTM infection at the Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, in the last 2 years, who were diagnosed using molecular tests. The specific details of clinical presentation, diagnostic methods and treatment regimens, along with outcomes, were reviewed retrospectively and summarized.
Results: The outcomes comprised 8 patients (5 females and 3 males) between 19 and 79 years. The signs and varied symptoms included fever, headache, cough and weakness. The confirmatory diagnosis was followed by Polymerase chain reaction (PCR) for NTM, biopsy from the site, such as abdominal and vertebrae and pleural fluid analysis. Most patients showed significant clinical improvement after the diagnosis and appropriate treatment.
Conclusions: This case series highlights the diverse clinical manifestations of NTM infections at extrapulmonary sites, emphasizing the importance of early diagnosis and appropriate management. Clinicians should maintain a high index of suspicion for NTM infections, especially in atypical presentations and immunocompromised patients.

Keywords: Non tubercular mycobacteria, Polymerase chain reaction, Extrapulmonary sites

INTRODUCTION

Non-tuberculous mycobacteria (NTM), often denoted as atypical mycobacteria, comprise a group of potentially opportunistic organisms leading to pulmonary and extrapulmonary infections, encompassing a variety of species, including *Mycobacterium avium*, Mycobacterium intracellulare and Mycobacterium abscesses and various others.[1] Individuals are exposed to NTM via sources such as contaminated soil, water and the community and can be affected by healthcare environments.[2] These organisms are ubiquitous in the environment, mainly found in soil and water and they have been increasingly recognized as opportunistic pathogens, particularly in individuals with compromised immune systems.[1,2] Individuals have shown an association with various climate factors and trace elements in water. In contrast, community-associated NTM infections have been linked to exposures such as tattoos and hot tubs. With the growing burden of disease, infections due to these organisms have led to increased hospitalizations, causing high morbidity and mortality due to various factors, such as the slow cultural growth of these

NTM organisms, the presence of some underlying conditions in these patients leading to compromised immune status and a varied clinical course of disease.[3] This is further complicated by its treatment regimen and increasing antibiotic resistance. While pulmonary infections due to NTM are well-documented and studied, their capacity to cause extrapulmonary disease is gaining high recognition, especially among populations with chronic lung disease, diabetes or those undergoing immunosuppressive therapy.[4] This case series aims to shed some light on the clinical manifestations, diagnostic challenges and management strategies for NTM infections at extrapulmonary sites through the presentation of eight different cases. Informed written consent was taken from all the patients. The study was approved by institutional research and ethical committees.

CASE SERIES

Case 1

Patient profile

A 19 years old female presented with an acute history of severe headache, low-grade fever, neck stiffness and pain since 2 months. There was no significant past medical or surgical history. No history of immunosuppressive therapy or chronic illnesses.

Diagnosis

A non-contrast CT of the head was performed, which was normal. CSF analysis revealed glucose levels of 45 mg/dL, indicating the possibility of infection, protein levels elevated to 110 mg/dL and a negative molecular test for tuberculosis. Polymerase chain reaction(PCR) for NTM in CSF was positive, confirming the diagnosis.

Treatment and outcome

The patient was started on a regimen that included macrolides and rifampicin. After one year of treatment, she demonstrated complete resolution of symptoms, with no signs of recurrence.

Case 2

Patient profile

A 58 years old male presenting with generalized weakness and progressive shortness of breath for one month. There was no prior history of pulmonary disease. He denied smoking and any past episodes of similar symptoms. He had no known allergies.

Diagnosis

An echocardiogram revealed an ejection fraction of 25%, indicating heart failure. Chest X-ray suggested right hydropneumothorax. An intercostal drain (ICD) was inserted and pleural fluid analysis indicated exudative characteristics with an Adenosine deaminase level of 41. PCR for NTM in the pleural fluid was positive.

Treatment and outcome

The patient received a combination of clarithromycin, ethambutol and modified tubercular regime, leading to significant clinical improvement during follow-up and complete resolution.

Case 3

Patient profile

A 49 years old female presented with persistent low backache for one year. There was no neurological deficit. She did not have a fever, loss of weight or loss of appetite. There were no previous gastrointestinal disorders and no history of surgeries. She had no known comorbidities. She was a non-smoker and a non-alcoholic.

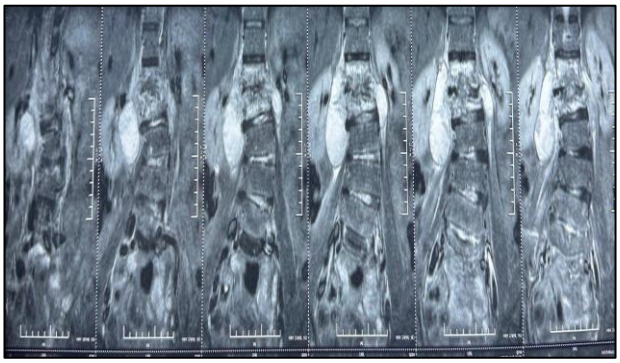

Figure 1: MRI Spine suggestive of thick collection in L2-L3.

Radiological imaging suggested a collection in the L2 and L3 vertebrae (Figure 1). A biopsy confirmed NTM growth.

Treatment and outcome

The patient was treated with a targeted antibiotic regimen for 12 months, resulting in symptom resolution upon follow-up, with imaging confirming the resolution of the collection.

Case 4

Patient profile

A 21 years old female presented with abdominal pain, nausea, vomiting, decreased urine output and anorexia for two months. Additionally, there were no signs of fever, weight loss or changes in bowel habits.

There were no significant past medical conditions reported, no previous hospitalizations and no known allergies. She denied any recent travel or new medications.

Diagnosis

Examination revealed pallor, icterus and generalized anasarca. Imaging suggested an intra-abdominal mass (Figure 2). Ascitic fluid analysis indicated a low serum-ascites albumin gradient (SAAG) and high protein levels. A biopsy was performed; unfortunately, the patient expired three days after admission due to severe metabolic acidosis and secondary bacterial peritonitis. The biopsy results were later found to be positive for NTM.

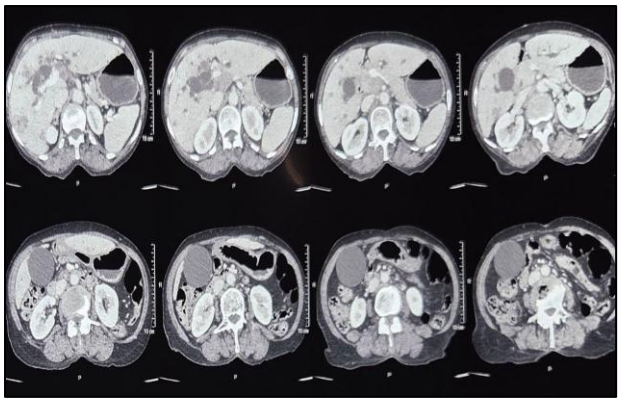

Figure 2: CT abdomen suggestive of intra-abdominal mass with ascites.

Outcome

This case underscores the challenges posed by delayed diagnosis due to slow culture growth and the advanced nature of the disease.

Case 5

Patient profile

A 44 years old male presented with haemoptysis and chest pain for 2 months along with constitutional symptoms. The patient denied any history of recent travel, exposure to tuberculosis or other infectious diseases, smoking or significant tobacco use or history of pulmonary disease or chronic cough. There was no family history of lung disease or cancer. There were no occupational exposures or hazardous environments.

Diagnosis

High-resolution computed tomogram of the thorax indicated bilateral consolidation with left empyema (Figure 3). Bronchoscopy was negative for tuberculosis; however, pleural fluid analysis confirmed NTM via PCR.

Treatment and outcome

The patient received appropriate therapy, resulting in resolution of symptoms as well as radiology.

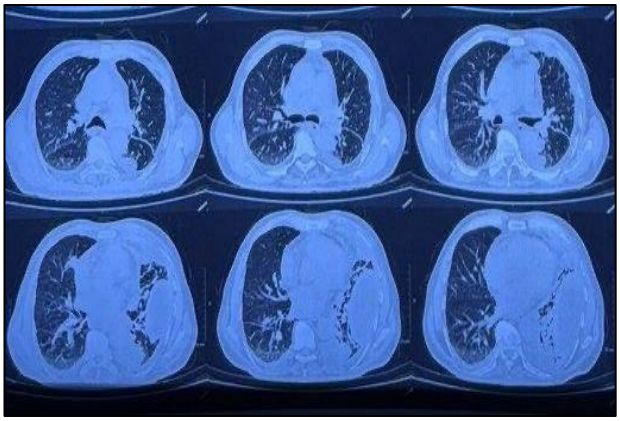

Figure 3: HRCT thorax suggestive of bilateral consolidation with empyema.

Case 6

Patient profile

A 79 years old female presented with generalized weakness, cough, weight loss and low-grade fever for four weeks. no previous history of chronic respiratory diseases, no recent travel or exposure to sick individuals, no significant past medical history such as diabetes or heart disease, no history of smoking or exposure to second hand smoke and no recent surgeries or hospitalizations. There are also no signs of bacterial infections, allergies or any recent changes in medications. She has not experienced night sweats, chest pain or hemoptysis.

Diagnosis

Computed tomogram of the thorax revealed a massive right effusion (Figure 4). Pleural fluid analysis indicated exudative effusion with an ADA level of 39.5. Medical thoracoscopy revealed diffuse whitish nodules and a biopsy of which confirmed NTM.

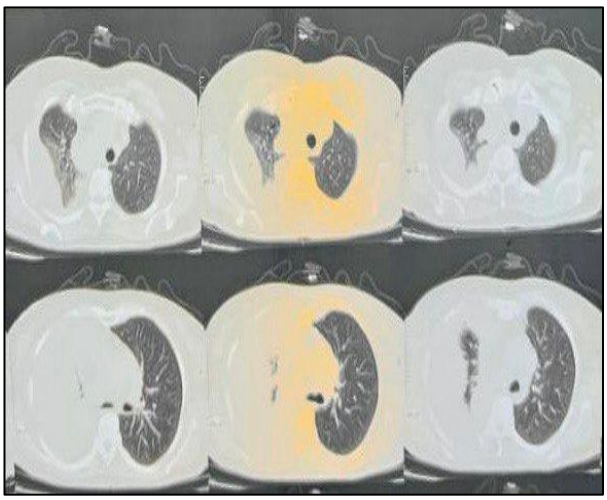

Figure 4: CT thorax suggestive of right sided effusion.

Treatment and outcome

Following antibiotic management, the patient showed significant improvement and was discharged after a prolonged hospital stay, with a healthy outcome.

Case 7

Patient profile

A 65 years old female presented with acute history of fever, shortness of breath and cough lasting one week. She was a known case of uncontrolled type 2 diabetes mellitus. The patient denied any recent travel, exposure to sick contacts or significant changes in her medications. There was no history of chest pain, hemoptysis or significant weight loss. She reported no allergies and had not experienced any recent hospitalizations or surgeries. Additionally, there was no history of smoking or substance abuse. Family history was unremarkable for respiratory diseases.

Diagnosis

Imaging suggested right moderate empyema (Figure 5). Medical thoracoscopy indicated a pus-filled pleural space, with biopsy results confirming NTM.

Figure 5: Right pleural effusion.

Treatment and outcome

The patient was managed with a tailored antibiotic regimen and showed significant clinical, radiological improvement in subsequent follow-ups.

Case 8

Patient profile

A 62 years old female presented with shortness of breath and chest pain for 1.5 months, with a history of uncontrolled diabetes and hypertension. The patient denied any recent respiratory infections or hospitalizations. She had no known allergies and reported no family history of lung diseases or cardiovascular issues. There was no recent travel or exposure to sick individuals and she denied smoking or using any tobacco products. No previous diagnosis of tuberculosis or other chronic respiratory conditions was noted.

Diagnosis

Chest radiography indicated right pleural effusion (Figure 6). Pleural fluid analysis revealed exudative characteristics and PCR for NTM was positive.

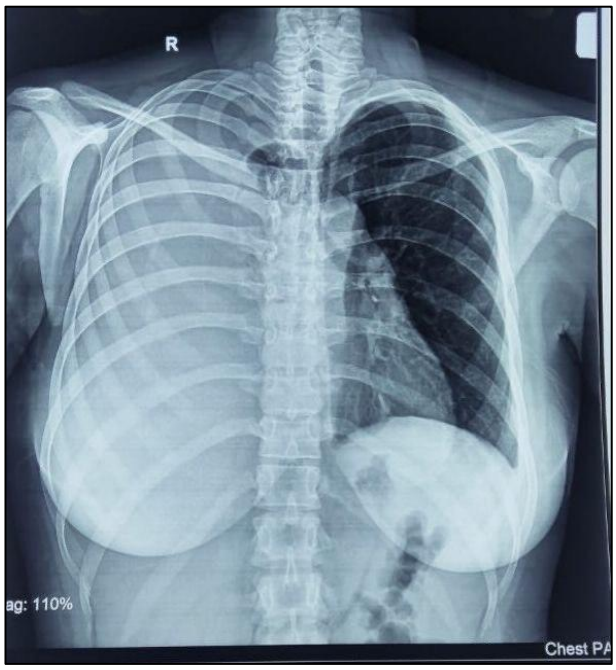

Figure 6: Chest X-ray suggestive of right massive effusion.

Treatment and outcome

The patient was started on therapy for NTM and exhibited marked improvement in symptoms, with follow-ups indicating resolution of the effusion with pleural thickening.

DISCUSSION

NTM are environmental organisms increasingly recognized as pathogens, particularly affecting the lungs. The prevalence of NTM pulmonary disease has risen, with Mycobacterium avium complex (MAC) and

Mycobacterium abscesses complex (MABC) being the most commonly isolated species. Diagnosis and treatment are challenging, requiring prolonged multidrug therapy and outcomes remain variable and recurrences are common due to either relapses or reinfections.[5] The emergence of NTM as significant pathogens in our clinical practice necessitates a comprehensive understanding of their epidemiology, their clinical manifestations, various diagnostic challenges and, most importantly, what treatment strategies to consider. This case series aimed at highlighting the complexity and the diversity of NTM infections at numerous extrapulmonary sites and shedding light on their clinical implications.

NTM infections present with a broad range of symptoms, often these mimic other diseases, especially Mycobacterium tuberculosis, leading to misdiagnosis at times and complicating management. In our series, patients exhibited symptoms ranging from neurological signs to respiratory distress and other systemic manifestations such as abdominal pain and ascites. This diversity requires clinicians to maintain a high index of suspicion for NTM in patients with atypical presentations, particularly immunocompromised individuals.[1,4] While TB is primarily transmitted through inhalation of aerosol droplets from symptomatic individuals, NTM infections are often acquired from environmental sources. Standardized TB treatments are generally effective, but NTM infections require species-specific therapies due to varying drug resistance.[6]

The study done in south India reported NTM infections which were identified in various clinical samples, particularly from pulmonary and extrapulmonary sites. Among the isolates, *Mycobacterium fortuitum* and *Mycobacterium chelonae* were the most common rapidly growing mycobacteria, while Mycobacterium avium complex was the predominant slow-growing species. However, this study also had a drawback similar to ours, including a relatively small sample size and the lack of advanced molecular techniques for species identification, which might have affected the accuracy of species differentiation. Additionally, antimicrobial susceptibility testing was not extensively explored, limiting treatment guidance.[7] A multicentred retrospective study done by Kim et al found that rapid-growing mycobacteria (RGM) were predominantly responsible for skin and soft tissue infections, whereas slow-growing mycobacteria (SGM) were mainly associated with bone and joint infections.[8] Female patients were more commonly affected by RGM infections, likely due to cosmetic procedures and local injections as predisposing factors. Antimicrobial susceptibility testing revealed that M. intracellular was consistently susceptible to clarithromycin, while RGM species showed varying resistance patterns, with most being susceptible to amikacin. These findings highlight the importance of species identification and tailored antimicrobial therapy for extrapulmonary NTM infections.[8] Maurya et al, investigated the occurrence of NTM in patients with extrapulmonary tuberculosis. Out of 62 NTM isolates identified, the most frequently occurring species were *Mycobacterium fortuitum* (25.8%), *Mycobacterium abscessus* (22.6%) and Mycobacterium intracellulare (16.1%).[9] The study also noted that a significant proportion of NTM isolates were from lymph node aspirates, highlighting the importance of considering NTM in differential diagnoses of lymphadenitis.[9]

Diagnosing NTM infections poses unique challenges due to their indolent nature and symptoms overlapping with various other conditions. Traditional culture methods can be slow and might at times yield negative results despite the presence of the pathogen.[2] For example, in Case 4, the diagnosis was confirmed posthumously, emphasizing the need for rapid and accurate diagnostic methods. A study conducted in Taiwan over a 12 years period investigated the clinical manifestations and outcomes of extrapulmonary infections caused by NTM. The study found that the most common sites of infection were lymph nodes, skin and soft tissues and bones and joints. Patients with immunosuppressive conditions, such as HIV infection or malignancy, were at higher risk for disseminated NTM infections, stating the importance of species identification and susceptibility testing to guide appropriate antimicrobial therapy.[10]

The clinical impact of NTM infections is particularly more pronounced in immunocompromised populations. The rising incidence of NTM infections correlates with increasing numbers of at-risk patients, requiring vigilant screening for the disease and early intervention strategies.[3] A case report of two AIDS patients who developed meningitis caused by NTM, where both patients succumbed to the illness, highlights the importance of promptly considering NTM meningitis in AIDS patients presenting with prolonged fever and neurological symptoms and initiating appropriate anti-NTM therapy when necessary.[11]

Molecular techniques, particularly PCR (Figure 7), have emerged as valuable tools for identifying NTM, allowing for quicker diagnosis compared to other traditional methods. Studies demonstrated that PCR can significantly reduce the time to diagnosis and improve treatment outcomes.[12] The use of advanced diagnostic techniques should be kept as a priority in patients with high clinical suspicion of NTM infections but negative culture results. The role of molecular assays like GenoType Mycobacterium CM/AS and MeltPro Myco for identifying Mycobacterium species has been reported. It has shown to have high sensitivity and specificity in differentiating MTBC from NTM with rapid and accurate identification of NTM species compared to different phenotypic and molecular diagnostic modalities. However, limitations such as the inability to identify all NTM species and potential misidentification due to genetic similarities among closely related species was seen.[13]

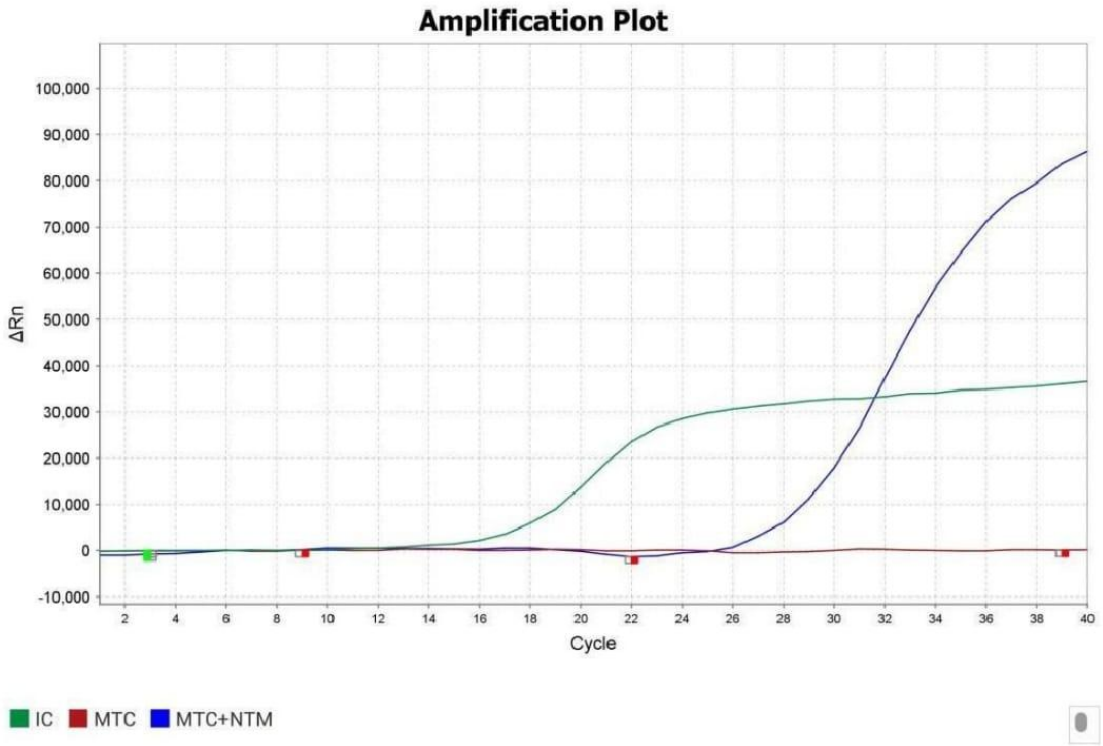

Figure 7: Melting Curve analysis of real time nested PCR for NTM in Sample.

IC–Internal Control, MTC-Mycobacterial TB Complex.

Management of NTM infections requires a prolonged antibiotic regimen tailored to the specific mycobacterial species. In our cases, patients were treated with combinations of macrolides, rifampicin and ethambutol, aligning with the latest guidelines.[1] The length of treatment varies and may extend beyond one year, particularly for disseminated or severe infections. Individualizing treatment based on the patient's clinical presentation and the NTM species is critical for success. Most patients in our series, fortunately, demonstrated significant clinical improvement following the targeted therapy they received. On the other hand, Case 4 illustrates the potential for severe and adverse outcomes in cases with extensive disease and sometimes delayed diagnosis.

Additionally, managing the underlying comorbidities, such as diabetes and immunosuppression, is essential. In Case 8, uncontrolled diabetes likely contributed to the patient's delayed presentation and guarded prognosis. Comprehensive care addressing both the NTM infection and underlying conditions is vital for getting optimum outcomes. The increasing prevalence of NTM infections poses a significant public health challenge. Understanding the epidemiological trends and associated risk factors for NTM is crucial for effective prevention strategies. Enhanced awareness among healthcare providers about the risk factors and clinical presentations can help facilitate earlier diagnosis and treatment, potentially reducing morbidity and thus mortality. Public health initiatives aimed at educating the high-risk populations about NTM, include those with underlying chronic lung disease or immunocompromised status, as it can promote timely medical intervention and improve overall health outcomes.

The case series highlights the significant clinical implications of NTM infections at extrapulmonary sites, underscoring their complexity, diagnostic challenges and the need for timely intervention. The diverse presentations among the eight patients illustrate that NTM can affect various body systems, leading to conditions ranging from neurological symptoms to severe respiratory distress and abdominal complications. These varied manifestations necessitate a high level of clinical suspicion, particularly in immunocompromised individuals or those with pre-existing health conditions. Early and accurate diagnosis is critical for improving patient outcomes. Our series emphasizes the limitations of traditional diagnostic methods, such as cultures, which can be slow and unreliable. The successful application of molecular techniques, particularly PCR, was instrumental in confirming diagnoses in several cases, thereby facilitating prompt treatment initiation. This reinforces the importance of incorporating advanced diagnostic modalities in clinical practice, especially in patients presenting with atypical symptoms. The treatment of NTM infections requires a tailored approach, often involving prolonged antibiotic regimens that address the specific mycobacterial species identified. The successful management of most patients in our series demonstrates the potential for positive outcomes when appropriate therapy is initiated. However, cases like that of the 21 years old female who succumbed to severe complications underscore the risks associated with delayed

diagnosis and the aggressive nature of advanced infections.

Public health awareness is paramount, as the incidence of NTM infections continues to rise globally. Healthcare providers must be educated about the risk factors, clinical presentations and effective management strategies for NTM infections to ensure early detection and treatment. Furthermore, targeted public health initiatives aimed at high-risk populations can help mitigate the impact of these infections.

This study had some limitations. First, diagnosis was based upon PCR detection of NTM and isolation of individual species couldn't be done. Antimicrobial susceptibility testing was also lacking, which may have led to ineffective treatment of the disease. However, as patients were evaluated on follow-up, none showed worsening or progression of the disease.

CONCLUSION

This case series not only enriches the understanding of NTM infections at extrapulmonary sites but also calls for ongoing research to further elucidate the epidemiology, pathogenesis and optimal treatment protocols. Continued efforts in these areas will be vital for improving patient care and outcomes in those affected by these increasingly recognized pathogens.

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