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Case Report

Challenges of diagnosing and treating non-tuberculous mycobacterial pulmonary disease [NTM-PD]: A case series

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ABSTRACT

Non-tuberculous mycobacterial pulmonary disease (NTM-PD) may simulate Pulmonary Tuberculosis (PTB) in its clinical and radiological expression posing a diagnostic dilemma and challenge to the treating physician, especially in high TB prevalent countries. Though recent emerging data indicates inter-human transmission, infection with non-tuberculous mycobacteria (NTM) is commonly acquired from the environmental sources [1]. NTM can produce disease not only in immunocompromised populations but also in healthy individuals leading to significant morbidity and mortality [2]. Unlike PTB, NTM-PD is usually difficult to confirm and speciate in resource limited clinical settings and high TB endemic countries due to non-availability, poor accessibility and affordability to a specific culture facility. Apart from diagnostic challenges, adverse drug effects with treatment leading to non-adherence are another vexing problem. We present here case descriptions of four patients of NTM-PD, confirmed by culture isolates, one was a rapid grower and the other three were slow growers. All four patients were treated with available guideline-based treatment protocols and followed up.

1. Introduction

NTM are environmental opportunistic organisms found in the soil, dust and water including its natural resources. Yet, NTM-PD is caused by relatively few species of NTM [3]. NTM represent about 190 species and subspecies and can produce disease in humans of all ages [4]. Worldwide, various population-based data and studies indicate a high and increasing prevalence of NTM-PD. Improved diagnostics and laboratory methodologies along with increased awareness among physicians might be contributory for the higher prevalence reported. Pulmonary disease (PD) is the most common clinical presentation of NTM infection accounting for 80 to 90% of all NTM-associated diseases [5]. The annual prevalence rate of NTM-PD varies in different regions ranging from 0.2 to 9.8/100,000 population. This may not reflect the true prevalence due to lack of consistent reporting and NTM infection not being notifiable in many countries. Period prevalence in studies including all ages was between 9 and 41/100,000. In all studies, *Mycobacterium avium* complex (MAC) was the most common (64%–85% of cases) cause of NTM-PD [6,7].

Various factors including pre-existing lung diseases, immunosuppressive therapies and interaction with environmental conditions may predispose to NTM-PD. Amongst medical host factors, structural lung diseases like COPD, bronchiectasis, prior infections, e.g. PTB and recently identified risk factors including thoracic skeletal abnormalities, viz., scoliosis, kyphosis, and pectus excavatum and low body mass index are some of the predisposing factors associated with NTM-PD. Recent biologics in the treatment of autoimmune disorders like rheumatoid arthritis along with systemic glucocorticoids might also predispose to NTM-PD [8–10]. Environmental factors like warm, humid climatic conditions (saturated vapor pressure) in various geographical regions may add a four-fold increased risk of infection of any NTM species [11].

The overall isolation rate of NTM reported in India ranges from 0.5% to 8.6% with a higher prevalence reported from south India [12]. In a single institutional study from Mumbai, India, 67 of 103 (65.0%) patients had pulmonary NTM isolates [13]. NTM isolation rate of 3.5% has been reported among HIV- negative (immunocompetent) patients in India [12].

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Table 1
Clinical Profile of The Study Subjects.

Case Characteristics	CASE 1	CASE 2	CASE 3	CASE 4
Sex/age in years	F/70	F/38	F/30	F/68
Fever	Present	Present	Present	Present
Cough	Productive cough (on and off) since 2 years	Productive cough with three episodes of minimal hemoptysis for 3 months	Productive cough with mucoid expectoration since 2 months	Increasing cough with purulent expectoration since 5 months
Shortness of breath	mMRC Grade II for 2 years [19].	Episodic, seasonal increasing since 3 months	–	mMRC Grade II for 5 months [19].
Loss of appetite	Present	Present	Present	Present
Loss of weight	Present	Present	Present	Present
History of TB	PTB 2 years ago	PTB 17 years and 4 years ago	PTB 2 years ago	PTB 10 years ago
History of Anti-tuberculous treatment (ATT) use	For 6 months, 2 years ago	For 6 months and 9 months, 17 years and 4 years ago respectively	For 6 months, 2 years ago	For 6 months 10 years ago, ATT use on and off from 2 years (irregularly)
Co-morbidities (if any)	Asthma	Allergic Rhinitis, Asthma	Patient has no co-morbidities	COPD
Drugs used for Co-morbidities	Salmeterol-Fluticasone Inhalation (twice daily)	Fluticasone Nasal spray (once daily); Budesonide-Formoterol inhalation (twice daily)	–	Formoterol-Budesonide Inhalation (twice daily) on as needed basis

Thus, it is a harbinger that healthcare providers will be encountering NTM-PD more frequently in the coming years, as noted in the recent clinical practice guidelines [4]. In patients with previous history of treatment for PTB, recent persistent symptoms with smear AFB (acid-fast bacilli) positivity may suggest relapse, reactivation or drug resistance to the treating physician, especially in high TB burden countries [14].

Improved awareness regarding NTM and a wider availability of nucleic acid amplification tests (NAAT)/ Xpert MTB/RIF assay (Cepheid GeneXpert System, Sunnyvale, US) resulted in differentiating NTM from MTB infections early on [15]. *Mycobacterium avium* complex (MAC) among slow growers and *Mycobacterium abscessus* complex amongst rapid growers are the most frequently encountered pathogens associated with NTM-PD, accounting for up to 95% of total cases reported [16]. Prior to molecular tests, standard way of diagnosing NTM was culture followed by biochemical testing. Newer molecular identification

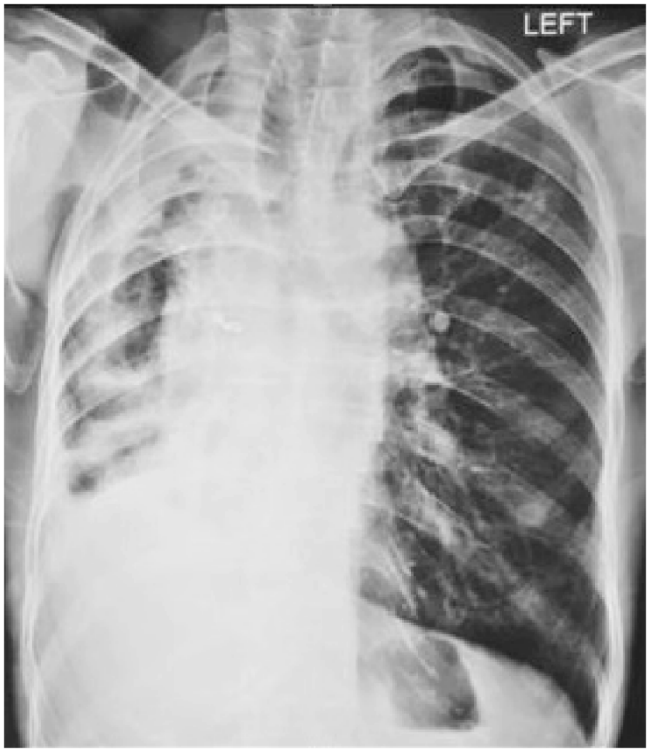

Fig. 1. Case-1: Chest X-ray PA view shows loss of lung volume in right hemithorax with elevated right hemi-diaphragm, rib crowding and ipsilateral mediastinal shift. Multiple fibro-cavitary lesions are seen in the entire right lung associated with upper lobe collapse and right basal pleural thickening.

Table 2
Investigation Profile of Study Subject.

Case Characteristics	CASE 1	CASE 2	CASE 3	CASE 4
Radiological features	Right Fibro-cavitary lung disease was evident on Chest X-ray & HRCT-Chest (Fig. 1, Fig. 2.)	Chest-X-ray and HRCT-Chest were suggestive of Left Fibro-cavitary lung disease (Fig. 3,Fig. 4, Fig. 5, Fig. 6)	Chest-X-ray was suggestive of Right Fibro-cavitary lung disease (Fig. 7,Fig. 8)	Right upper lobe cavitation with bilateral fibrosis was seen on Chest X-ray and HRCT chest (Fig. 9, Fig. 10)
ESR (in 1sthr)	60 mm	84 mm	90 mm	74 mm
Microscopy on 3 consecutive sputum samples	Tested positive for AFB	Tested positive for AFB	Tested positive for AFB	Tested positive for AFB
Sputum sample for XpertMTB/RIF assay	*Mycobacterium tuberculosis* not detected	*Mycobacterium tuberculosis* not detected	*Mycobacterium tuberculosis* not detected	*Mycobacterium tuberculosis* not detected
Sputum sample for Fluorometric BACTEC MGIT liquid culture	Growth of Mycobacteria within 7 days	Growth of Mycobacteria after 3 weeks	Growth of Mycobacteria after 3 weeks	Growth of Mycobacteria after 3 weeks
Identification of Mycobacteria by MPT64 antigen and growth characteristics on solid media.	Rapid grower Mycobacteria (RGM)	Slow grower Mycobacteria (SGM)	Slow grower Mycobacteria (SGM)	Slow grower Mycobacteria (SGM)
NTM Species identification	Not done	Not done	Not done	Not done
Subsequent AFB culture for NTM confirmation [5]	RGM confirmed in BAL fluid	SGM confirmed in two sputum samples	SGM confirmed in two sputum samples	SGM confirmed in BAL fluid

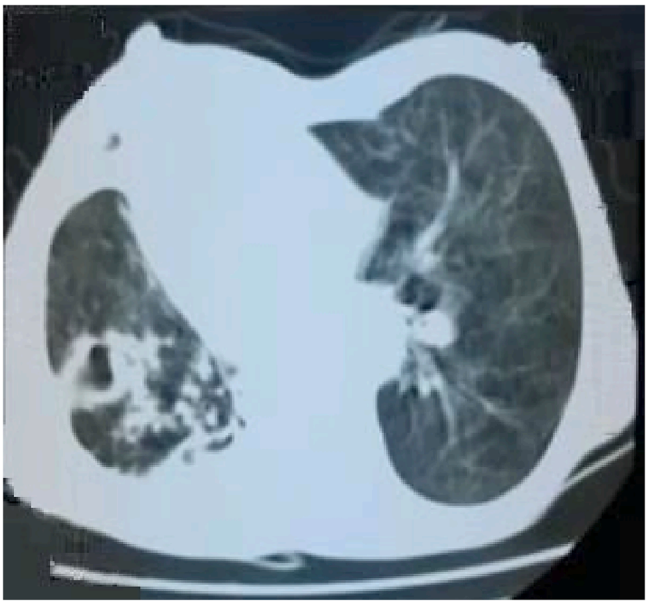

Fig. 2. Case-1: Axial HRCT at the level of mid-thorax reveals collapsed upper lobe, cavities and small nodules in the right lower lobe and ipsilateral mediastinal shift.

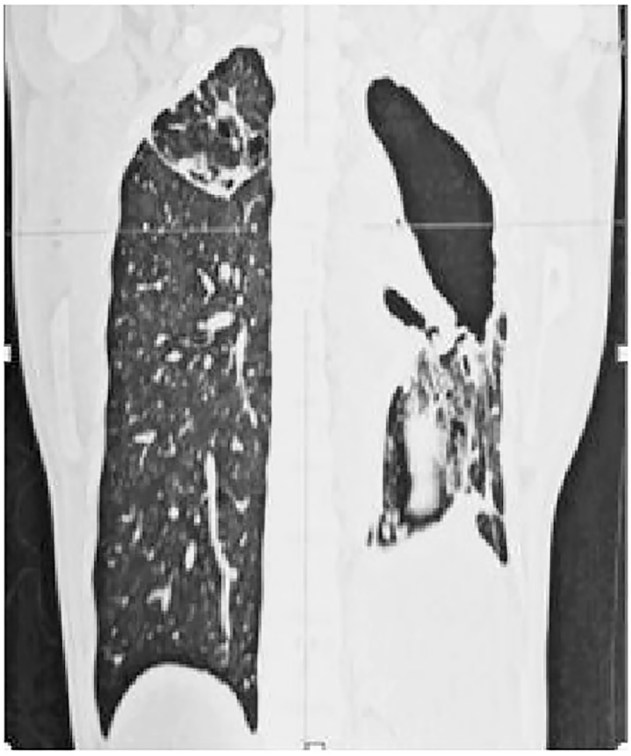

Fig. 3. Case-2: Coronal HRCT of the chest reveal fibro-cavitary lesions in the right upper lobe with partial loss of volume. A large cavity is seen in left upper lobe with severe fibrotic lesions in the left lower lobe associated with loss of volume in left hemithorax.

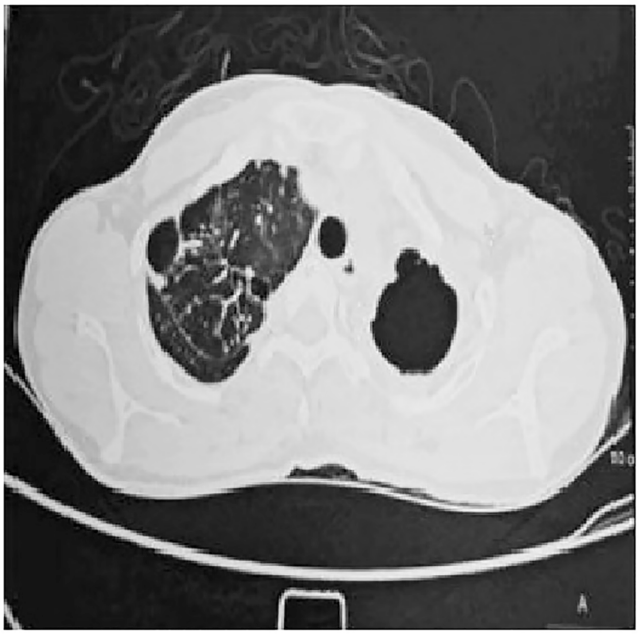

Fig. 4. Case-2: Axial HRCT of the chest reveal fibro-cavitary lesions in the right upper lobe with partial loss of volume. A large cavity is seen in left upper lobe with severe fibrotic lesions in the left lower lobe associated with loss of volume in left hemithorax.

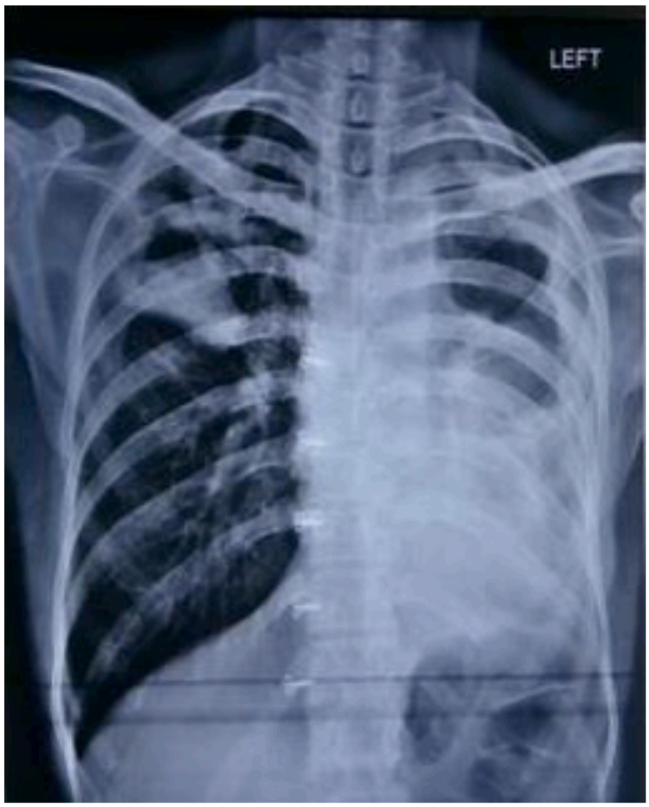

Fig. 5. Case-2: Chest radiograph PA view reveals consolidation in the right upper and mid lung zones, large cavity in the left upper lung zone, collapse consolidation in the left mid and lower zone and volume loss in the left hemithorax.

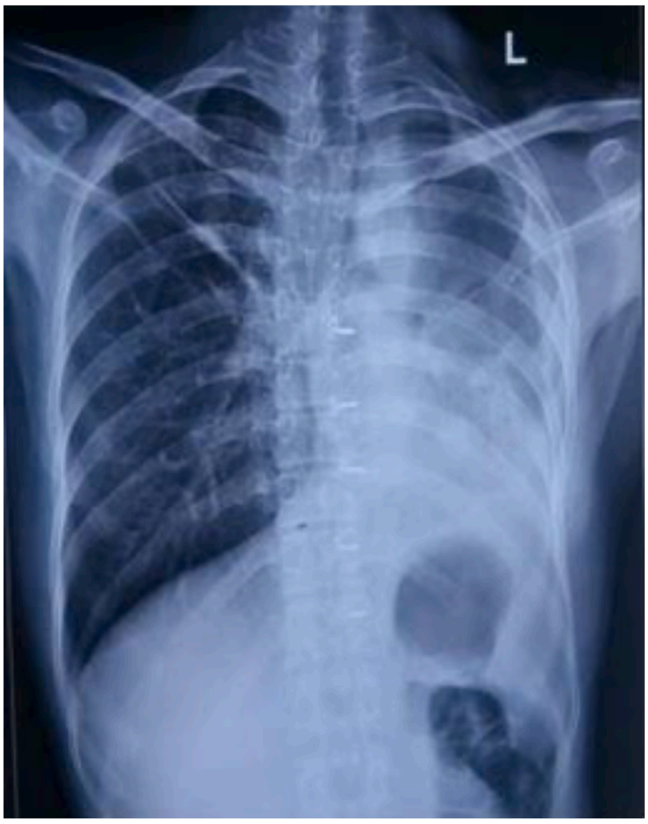

Fig. 6. Case-2: Chest radiograph PA view after completion of treatment reveals significant resolution of the right upper and mid zone consolidations.

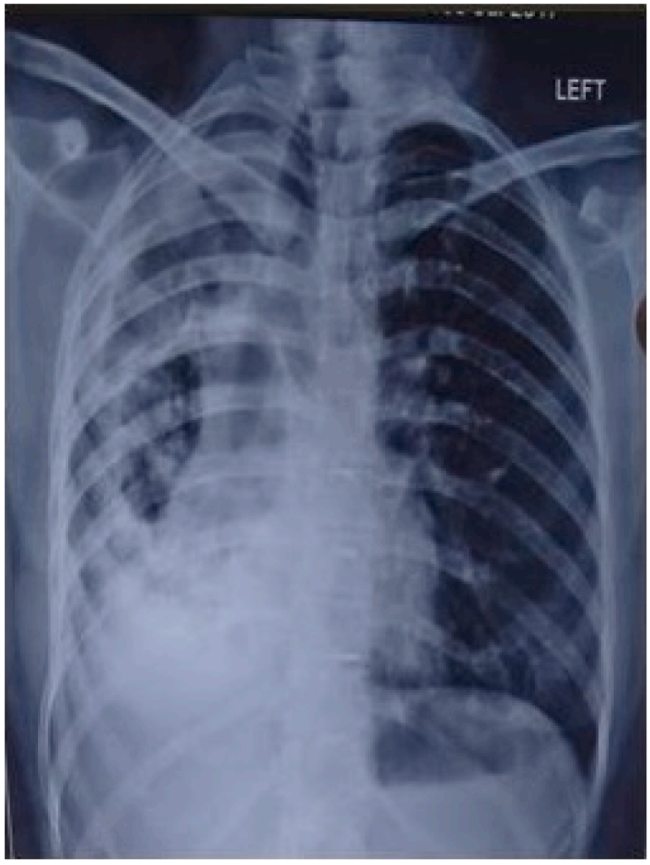

Fig. 7. Case-3: Chest radiograph PA view before commencement of treatment reveals fibro-cavitary lesions in the right lung, multiple nodules in the right mid and lower zones and loss of volume in right hemi-thorax.

methods, viz., 16sRNA sequencing, line probe assay, and Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) are the preferred methods for speciation now [17,18]. Molecular testing enabled an early diagnosis of NTM-PD and differentiation from *Mycobacterium Tuberculosis* Complex (MTBC). Specific treatment for NTM-PD can be instituted after species identification since newer rapid tests can decrease the delay in initiation of treatment thus lessening morbidity and mortality.

2. Design

Present study consisting of four patients of NTM-PD carried on in our single centre-Prathima Institute of Medical Sciences, Karimnagar, India between February 2017 and March 2021 is being reported. Prior IRB permission to conduct this study was obtained before registering the patients in the present case series [IRB approval Number: IEC/PIMS/2017/004]. A written informed consent was obtained from the patients for publication of this article.

3. Case reports

Herein we present four patients of NTM-PD having respiratory symptoms with constitutional disturbances like loss of appetite and loss of weight and a history of previously treated Pulmonary Tuberculosis (PTB). Demographic, diagnostic and treatment descriptions of these patients are shown in Table 1, 2 and 3 respectively.

As per Revised National TB control program (RNTCP) guidelines of India, these four patients can be considered as presumptive Drug resistant TB (DR-TB) cases for which Nucleic acid amplification test (NAAT) / Xpert MTB/RIF assay must be performed to rule out Drug resistant PTB (DR-TB) [20].

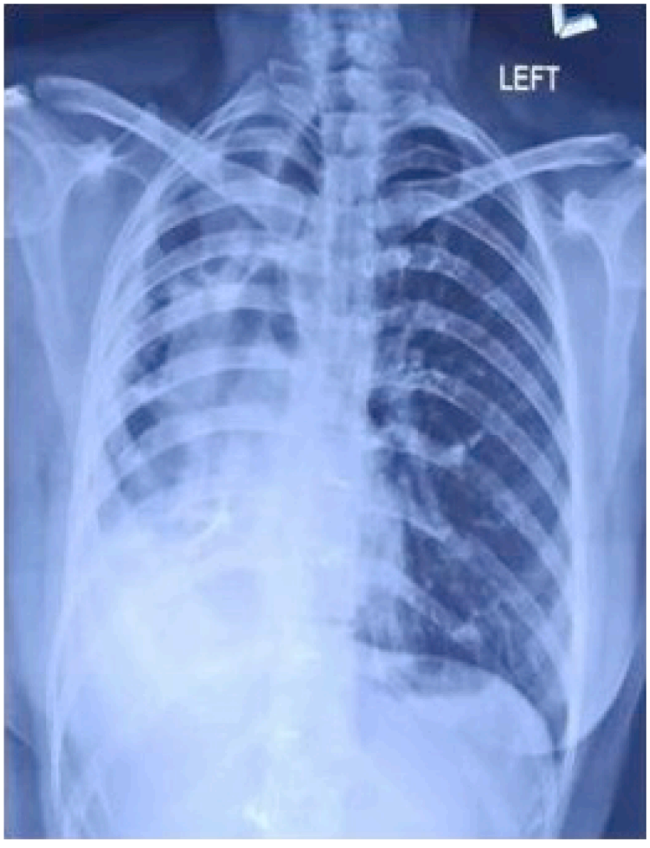

Fig. 8. Case-3: Chest radiograph PA view after completion of treatment reveals significant resolution of right lung nodular lesions.

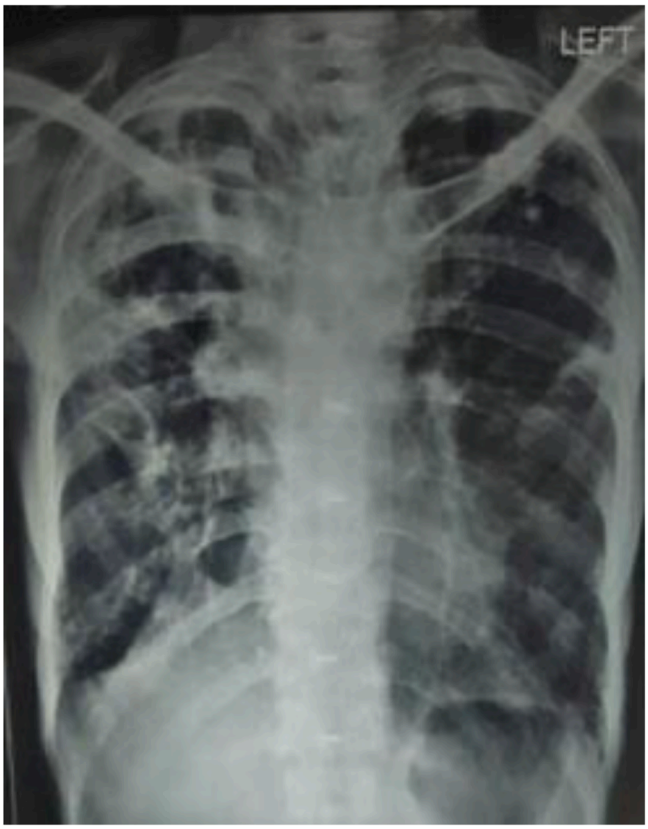

Fig. 9. Case-4: Chest radiograph PA view shows right upper zone cavities and extensive bilateral fibrotic bands.

Our patients had sputum smear positive for acid fast bacilli (AFB) persistently but *Mycobacterium tuberculosis* was not detected on Xpert MTB/RIF assay. This raised a diagnostic dilemma that was resolved by growth of NTM on AFB culture. All our patients were symptomatic. Based on the clinico-radiological profiles of the patients with a positive mycobacteriological data, treatment regimen was framed. The NTM treatment regimens were guideline based [21]. The following is the description of treatment regimens assigned to each of our patients and the clinical outcomes (Table 3).

4. Discussion

For decades, diagnosis, relapse and resistance of PTB with *Mycobacterium tuberculosis* was and is a vexing problem for the clinicians in high TB-endemic countries like India. Hitherto, this aspect of management approach was based on smear AFB from sputum and other respiratory specimens. Even today, culture AFB facility to be available uniformly in the National program is a far cry. Advent of Xpert MTB/RIF assay fulfilled this deficiency of culture facility to a greater extent in treating Tuberculosis (TB).

For confirmation of PTB or otherwise in high TB endemic countries, clinicians rely on sputum microscopy and chest radiograph which cannot differentiate PTB from NTM-PD. Although culture remains the gold standard for diagnosis, identification using nucleic acid amplification testing (NAAT), viz., Xpert MTB/RIF assay, which has a sensitivity of 95.7% and specificity of 99.3% for MTB, aids to detect *Mycobacterium Tuberculosis* and drug resistant TB and a negative result in suspecting NTM-PD. Thus, patients of presumed DR-TB who are smear positive, NAAT (Xpert MTB/RIF assay) negative, Line probe assay-Tuberculosis Band (LPA-TUB) absent with or without R resistance need to be evaluated for NTM-PD. This enables specific and prompt initiation of therapy for NTM-PD [22,20].

The two most important risk factors for NTM-PD are presence of structural lung disease (Cystic Fibrosis, COPD, history of PTB, etc.) and Immunosuppression (HIV, Transplantation, Primary Immunodeficiency, etc.) [23,3]. In patients with Mycobacterium avium complex pulmonary disease (MAC-PD) serum adiponectin levels were found to be inappropriately increased especially in individuals with lower BMI values. A similar correlation was not found with serum leptin levels in MAC-PD and control subjects. Increased levels of adiponectin in slender individuals might have a pro-inflammatory effect and play a role in its pathogenesis [24]. All our patients were immunocompetent, had a low BMI with a past history of treated pulmonary tuberculosis and were at some point of time involved with agriculture, suggesting that environmental exposure in these individuals might have predisposed them to NTM-PD, since contaminated soil and water supplies are considered an important source for NTM causing human infections [17].

Diagnosis of NTM-PD is usually delayed, in view of its indolent nature with nonspecific clinical features. Frequent coexistence of NTM-PD with underlying and predisposing conditions like COPD or Bronchiectasis and the latter presenting with similar clinical expressions, may further add to the diagnostic dilemma [25]. Minimum evaluation needed to diagnose NTM-PD, when suspected, requires: appropriate exclusion of other disorders in a patient with pulmonary symptoms, chest radiograph or HRCT chest suggestive of characteristic radiological findings (cavitary or multifocal nodulo-bronchiectatic lesions) and three consecutive, early morning sputum samples for AFB analysis [20,5].

Microbiologic criteria for the diagnosis of NTM-PD needs: Two positive cultures of the sputum specimens or one positive culture of broncho alveolar lavage fluid (BAL) / washings; compatible histopathology

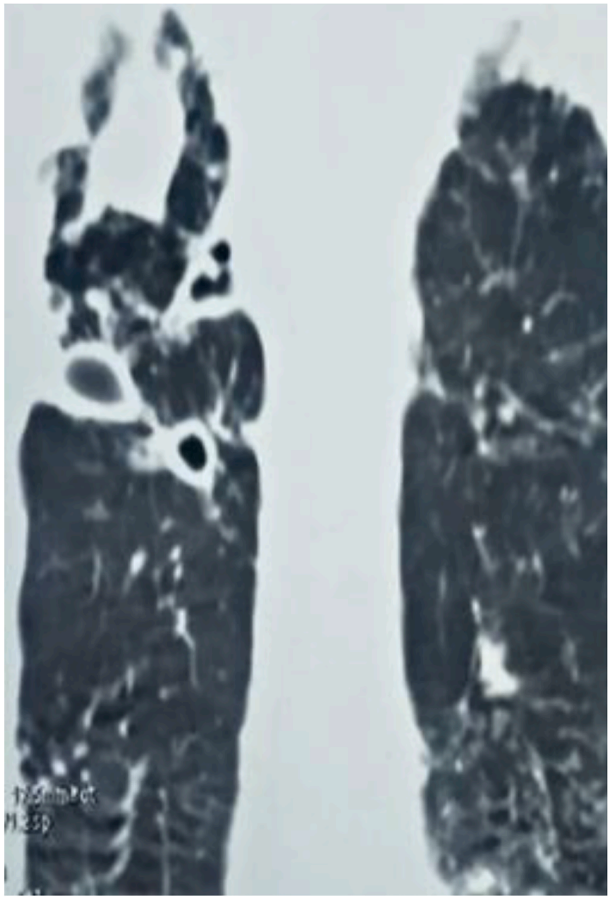

Fig. 10. Case-4: HRCT Chest coronal section shows right upper lobe consolidation, cavities in the superior segment of the right lower lobe and bronchiectasis with fibrotic lesions in the left lower lobe.

Table 3
Treatment Profile of Study Subjects.

Case Characteristics	CASE 1	CASE 2	CASE 3	CASE 4
NTM growth assumed to be:	RGM: *Mycobacterium abscessus* complex (MABC)	SGM: *Mycobacterium avium* complex(MAC)	SGM: *Mycobacterium avium* complex (MAC)	SGM: *Mycobacterium avium* complex (MAC)
Empirical treatment regimen started	Clarithromycin + Moxifloxacin (tablets) + Injection Amikacin (discontinued after 3 months)	Azithromycin + Rifampicin + Ethambutol (tablets) + Injection Amikacin (for 4 months)	Azithromycin + Rifampicin + Ethambutol (tablets) + Injection Amikacin (for 6 months)	Azithromycin + Rifampicin + Ethambutol (tablets) + Injection Amikacin (for 4 months)
Initial treatment response	Symptomatic improvement after 3 months of therapy	Clinico-radiological resolution seen during treatment course	Symptomatic improvement after 6 months of therapy	Symptomatic improvement after 2 months of therapy
AFB cultures during treatment course showed	Culture conversion noted at 6 months of treatment and culture was positive again at 9thmonth during treatment.	Culture conversion noted at 6 months, subsequent culture after 12 months of treatment was negative.	Culture conversion noted at 6 months, subsequent culture after 12 months of treatment was negative.	Culture conversion noted at 6 months, subsequent culture after 12 months of treatment was negative.
Subsequent culture conversion during therapy was not seen due to	Refractory NTM-PD considered. Moxifloxacin resistance seen on subsequent antimicrobial susceptibility testing (AST).	–	–	–
Redesigned therapeutic regimen	Amikacin + Tigecycline + Imipenem (Injections) + Clarithromycin (tablets) for 4 weeks [Initiation phase]	–	–	–
Final treatment response	Patient discontinued treatment due to severe nausea, vomiting and thrombo-phlebitis as a result of repeated injections, within first 2 weeks. Refused further continuation of treatment and left against medical advice	Treatment was continued for 12 months after culture conversion and the patient is currently in remission	Treatment was continued for 12 months after culture conversion and the patient is currently in remission	Treatment just concluded at the end of 12 months after culture conversion

(granulomatous inflammation) of transbronchial or any other lung biopsy with culture positive for NTM [21,20]. NTM-PD is manifested by two main radiographic patterns: (i) an upper lobe fibro-cavitary pattern that occurs predominantly in men with an underlying lung disease and (ii) a nodular-bronchiectasis pattern involving right middle lobe and lingula that is more common in women having no clear risk factors [26]. All the patients in the present study had fibro-cavitary disease with one of them having both fibro-cavitary and nodular lesions.

Institution of therapy for NTM-PD is a decision based on potential risks and benefits of therapy in symptomatic patients. Making a diagnosis of NTM-PD does not per se necessitate institution of therapy [25]. Identification of NTM species is ideal and allows for assessment of clinical significance, prognosis, and expected antimicrobial resistance necessary for guiding an empirical therapeutic strategy [2]. The aim of diagnosis should be to formulate an appropriate treatment regimen preferably based on the susceptibility testing. But in view of discrepancies between in vitro and in vivo drug susceptibility results and absence of definitive consensus for guidelines regarding drug sensitivity test correlations, one may have to cautiously choose an empirical treatment approach initially, when accessibility and affordability to such facility is not possible. However, susceptibility-based treatment regimens are to be preferred over empiric therapies whenever such facility for AST is available.

The management of NTM is usually guided by the ATS/IDSA or the BTS guidelines and is challenging because of antibiotic resistance of NTM species attributed to their biofilm production, requirement of multi-drug regimens for an extended period, frequent intolerance of the prescribed regimens and relatively high frequency of relapse and/or reinfection [5,21,27]. In the present case series, three of the four patients reported positive for NTM-slow-growers. During evaluation of these patients there was no accessibility to the nearby facility for speciation. The attendant cost constraints also prevented us from performing speciation routinely. Global epidemiological data noted, in most of the studies, MAC was the most common species complex (up to 85% of cases) followed by *M. abscessus/chelonae* (3–13%). Based on these observations we treated our patients of 'slow growers' for MAC and 'Rapid growing mycobacteria' (RGM) for *M.abscessus* complex [7]. Predisposition to and progression of NTM disease is reported to be associated with poor nutritional status. Hence, dietary consultation can be recommended in NTM-PD because poor nutritional status is associated with increased adverse effects and drug intolerance, thereby resulting in a poor therapeutic response. Likewise, vitamin deficiencies, especially Vitamin A, are suggested to have been associated with NTM-PD [28–30]. These nutritional aspects were taken care of during the treatment of our patients.

Failure to achieve culture conversion after 6–12 months of therapy is defined as treatment failure [28]. Retreatment strategy would depend on Macrolide sensitivity of the isolate and if these patients are found to be intolerant to treatment or drug resistant, lung resection can be effective in controlling infection, provided the disease is localized [21]. In the present study, the three SGM patients achieved culture conversion and did not relapse during the follow up period. Patient with RGM discharged herself at request due to adverse drug effects.

5. Conclusion

In summary, PTB patients who are non-responders to standard ATT regimen should be evaluated for NTM-PD. As NTM are ubiquitous organisms, neither their mere isolation from pulmonary samples is sufficient evidence for the presence of NTM-PD nor is an indication for treatment. NTM-PD diagnosis requires integration of clinical, radiographic and microbiological criteria for prompt therapy. The patient's wish, affordability and ability to receive treatment as well as the goals of therapy should be discussed with patients prior to initiating treatment. These patient-centric aspects along with species identification and antimicrobial sensitivity testing (whenever available) needs to be considered an integral part of NTM-PD management. In some instances, viz., patients with mild signs and symptoms and those with potential for drug intolerance and those with RGM isolates less responsive to treatment (eg.*M. abscessus*), "watchful waiting" may be the preferred course of action [4].

To conclude, there is a need for increased awareness and clinical suspicion on the part of the treating physician and provision of improved mycobacteriology services to be incorporated into the National Programs. This facilitates institution of prompt evidence-based treatment options for NTM-PD which is extremely challenging in resource limited clinical practice.

Declaration of Competing Interest

The authors: No reported conflicts of interest. All authors have submitted the ICMJE form for Disclosure of Potential Conflicts of

Interest.

Acknowledgements

Nil.

Author contributions

Author Aditya Chindam helped in acquisition of data and provided the needed inputs on writing the manuscript and made multiple edits and suggestions in the preparation of this report. Authors Samanvitha Vengaldas and Vijetha Reddy Srigiri reviewed background information, and literature. Authors Umair Syed and Hemanth Kilaru provided inputs for the manuscript writing, its analysis and interpretation. Author Nagender Prasad Chenimilla's contribution was - drafting and revising it critically for important intellectual content, final approval of the version to be submitted. Author Satish Chandra Kilaru is involved in the conception and design of the study and drafting the main content of the article and is the corresponding author. Author Ekta Patil provided the Microbiological investigations and the necessary laboratory support for the study.

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