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Case Report

Microbiology Section

An Emerging Neglected Co-infection: *Aspergillus fumigatus* and *Mycobacterium gordonae* Co-infection in an Immunocompromised Patient

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ABSTRACT

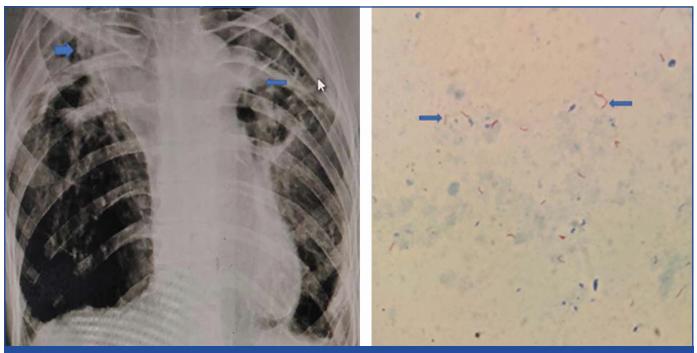
Non Tuberculous Mycobacteria (NTM) commonly affect the immunocompromised patients afflicted with chronic pulmonary disease and other opportunistic infections such as *Aspergillus* species. Although the symptoms and signs are similar for both, early laboratory diagnosis and treatment would reduce the duration of hospitalisation and unnecessary exposure to antimicrobials. Since NTM and *Aspergillus* species co-infection is an emerging trend, and delay in diagnosis and treatment can cause major complications, it is essential to clinically suspect the same, and this will help in early diagnosis of the infection, keeping in mind the delayed growth of NTM and *Aspergillus* species in culture and the time taken to identify the infecting organism. Here, an interesting case of an immunocompromised 63-year-old male patient with Chronic Obstructive Pulmonary Disease (COPD) on frequent treatment who had symptoms of cough with expectoration, breathlessness on exertion, malaise, loss of weight and apetite for three months is reported. The patient was conscious, oriented and cachectic with complaints of breathing difficulty at the time of admission. Considering the positive report of sputum for Acid Fast Bacilli (AFB) and negative GeneXpert report, the patient sample was tested by Polymerase Chain Reaction (PCR) for NTM which was positive. The patient was diagnosed with *Mycobacterium gordonae (M. gordonae)* and *Aspergillus fumigatus* co-infection.

Keywords: Chronic obstructive pulmonary disease, Genexpert, Non tuberculous mycobacteria, Pulmonary aspergillosis

CASE REPORT

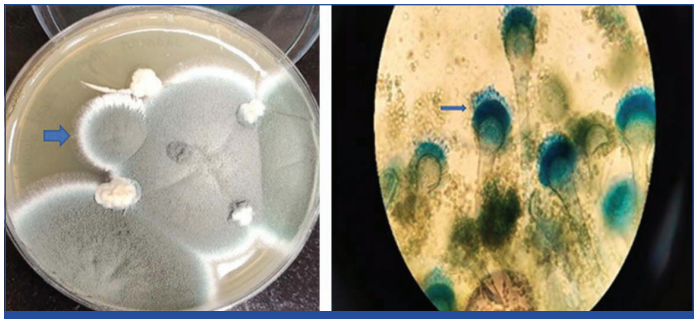
A 63-year-old male was admitted to the Pulmonology Department with complaints of cough with expectoration, breathlessness on exertion, loss of weight and appetite and malaise for the past three months. He gave no history of haemoptysis and fever. Patient was a chronic smoker with a known history of ischaemic heart disease with old myocardial infarction and post status percutaneous transluminal coronary angioplasty done in the year 2007. Right pleurectomy was done in the year 1990 due to alleged pneumothorax and was treated for three years. He developed COPD in the year 2015 for which he was hospitalised several times and underwent treatment at his native place. He had no history of systemic hypertension/type 2 diabetes mellitus.

At the time of admission, the patient was conscious, oriented and cachectic with complaints of breathing difficulty (SpO_2-92% in room air). On auscultation severe crepitations were noted bilaterally over the lung bases. Patient was admitted and was advised for echocardiogram, X-ray chest, High Resolution Computed Tomography (HRCT) (chest), routine blood investigations, sputum for AFB, Gram staining, AFB culture and fungal culture. Patient was started on broad spectrum antibiotic (Injection Ceftriaxone 1g i.v. BD), oxygen support and other supportive medications. Chest X-ray [Table/Fig-1] and HRCT revealed extensive fibrosis with traction bronchiectasis, cavity formation in both upper lobes, centrilobular nodules with tree in bud configuration in both lungs and extensive bullous emphysematous changes with associated destruction of lung parenchyma. Echocardiogram showed regional wall abnormalities, sclerosed aortic wall, Left Ventricle Ejection Fraction (LVEF)-45%, Pulmonary Arterial Systolic Pressure (PASP) was 55 mmHg and no evidence of pulmonary embolism. Three consequent sputum samples of the patient, collected on three days were positive for AFB by Ziehl Neelsen (ZN) method with a grade of 3+ [Table/Fig-2]. Sputum gram stain revealed pus cells more than 25 per low power field, plenty of gram positive cocci in pairs, short chains and occasional cluster while routine bacterial culture



[Table/Fig-1]: Chest X-Ray: B/L upper lobes showing fibrotic areas.
[Table/Fig-2]: ZN stain for acid fast bacilli from the patient's sputum sample. (Images from left to right)

of the sputum yielded normal flora of respiratory tract. Fungal culture on Sabouraud Dextrose Agar (SDA) yielded *Aspergillus fumigatus* after four days of incubation with colonies showing blue-green pigmentation [Table/Fig-3]. Lactophenol cotton blue mount demonstrated conidiophores with the characteristic features suggestive of *Aspergillus fumigatus* [Table/Fig-4]. Considering the HRCT report and the patient's symptoms, sputum sample was sent for GeneXpert, Interferon Gamma Release Assay (IGRA) and ZN stain for AFB. *Mycobacterium tuberculosis* was not detected by GeneXpert (Cepheid) and IGRA was negative which ruled out *Mycobacterium tuberculosis*. Lowenstein Jensen medium yielded no growth during the first week of culture. Considering the positive report of Sputum for AFB and negative GeneXpert report, the patient sample was tested by PCR for NTM which was positive. After two weeks of incubation, LJ medium yielded bright yellow colonies [Table/Fig-5] which were confirmed to be acid fast bacilli by Ziehl Neelsen (ZN) stain and then subjected to species identification by Matrix Assisted Laser Desorption/Ionisation Time-of-Flight Mass Spectrometry (MALDI-TOF-MS), which identified the colonies as *M. gordonae.*



[Table/Fig-3]: SDA (Sabouraud dextrose agar): bluish green pigmented mold, evident of *Aspergillus fumigatus*. **[Table/Fig-4]:** LPCB: The arrangement of conidiophores, phialides, and conidia shows typical characteristic evidence of *Aspergillus fumigatus*. (Images from left to right)

[Table/Fig-5]: Lowenstein Jensen Media: Yellow pigmented colonies of *M. gordonae*.

Aspergillus specific IgM, IgG, Precipitin, IgE, serum galactomannan assays were performed in view of the cavitary lesions on HRCT chest. Serum galactomannan, Serum IgE total antibody was negative, Aspergillosis IgG was positive indicating chronic pulmonary Aspergillosis. Patient was started on Capsule-rifampicin 450 mg (OD), Tab. isoniazid 300 mg (OD), Tab. Ethambutol 600 mg (OD), Tab. clarithromycin 500 mg (OD), Inj. amikacin 500 mg iv (OD), Tab. benadon 20 mg (OD), Tab. itraconazole 200 mg (BD). Patient improved symptomatically in a week, saturation improved to 97% in room air and was discharged. The patient was advised to continue the antitubercular drugs, macrolide, antifungal and the other supportive medications for a month until review. The patient's consent was obtained prior to publication.

DISCUSSION

Mycobacterium tuberculosis complex are a group of Mycobacteria that cause tuberculosis. NTM are a group of closely related mycobacteria that cause opportunistic lung disease in individuals with pre-existing pulmonary disease. *M. gordonae* was named after Ruth E. Gordon, belongs to the phylum Actinobacteria genus *Mycobacterium*. It is a scotochromogen (Runyoun classification of NTM), as it produces pigment when grown in dark and also under light. *M. gordonae* colonies are smooth, pasty and produce a yellow pigment and it is a slow grower taking approximately three weeks to appear on Lowenstein Jensen medium. In spite of being considered as a contaminant, there has been a continual increase of *M. gordonae* infection and pulmonary disease worldwide in both immunocompetent and immunocompromised patients. Also the prevalence of NTM species varies according to the geographical locations. *M. gordonae*, formerly called *Mycobacterium aquae* is ubiquitous and commonly present in aquatic environment [1]. It is known to be a common contaminant of tap water and clinical specimens. Since NTM exist as common environmental organism, the detection of these organisms in pulmonary specimen does not always denote the existence of the disease itself [2]. Therefore, in order to establish an accurate diagnosis, radiographic evidence and clinical findings plays a major role to establish an accurate diagnosis. Laboratory detection of NTM has improved with the advancement in detection methods and higher incidence of NTM [3]. Though being ubiquitous and harmless in nature, Chen L et al., has reported that *M. gordonae* produces clinically significant disease in immunocompetent adults as relevant to this case report [4].

Both Mycobacterium and Aspergillus species exists as opportunistic pathogens causing severe pulmonary manifestation. However, co-infection with these pathogens has been reported very rarely [5]. It remains difficult to differentiate the colonisation of these organisms in an active infection. Also requires prolonged treatment that is poorly tolerated and requires antimicrobials that can further lead to drug interactions and side-effects. The cavitary lesions also need surgical resection which can worsen the prognosis [6]. Also a significant rise in the mortality rate has been reported in patients with co-infection caused by NTM and Aspergillus species because of the complexity in the performance of antimicrobial susceptibility testing and unavailability of clinical breakpoints for many drugs for both the pathogens [7]. Inspite of being considered as a contaminant, there has been a continual increase of *M. gordonae* infection and pulmonary disease worldwide in both immunocompetent and immunocompromised patients. The environmental distribution of NTM clearly indicates that the organism most likely enters the human host by inhalation, ingestion or implantation. Nosocomial outbreaks due to *M. gordonae* are possible due to contamination of water supplies, dialysis solutions and medical equipment including bronchoscopes and endoscopes [8]. It is important to evaluate the clinical significance of NTM in clinical specimens when they are present in very minimal concentration [9]. Patients with chronic pulmonary aspergillosis and NTM lung disease should be appropriately diagnosed by the clinicians, as it may worsen the clinical outcome in these patients when compared to those infected with NTM only. There is a higher frequency of pneumothorax in patients with underlying NTM lung disease. A similar case report, *Aspergillus fumigatus* and *M. gordonae* co-infection was reported by Kosmidis C and Denning DW [10]. As discussed by Chang HY et al. *M. gordonae* though being commonly known as a water contaminant is now emerging as a pathogen affecting both immunocompromised and immunocompetent patients [11]. Multi-antimicrobial combination such as antitubercular drugs along with macrolides and adequate source control will have good therapeutic effect for patients with *M. gordonae* infection as seen in index case. NTM disease requires various diagnostic parameters and the slow growing characteristic of *M. gordonae* can further delay the species identification. Therefore, detection of NTM species by an automated Thermally-assisted Hydrolysis and Methylation followed by Gas Chromatography-Mass Spectrometry (THM-GC-MS) [12] or a real time RT-PCR can help in monitoring the disease progress of the patient and to modify the drug dose. Usually, the treatment of NTM varies from 12-18 months depending on the clinical symptoms of the patient. For current case, the patient was advised Capsule-rifampicin 450 mg (OD), Tab. isoniazid 300 mg (OD), Tab. ethambutol 600 mg (OD), Tab. clarithromycin 500 mg (OD), Tab. benadon 20 mg (OD), for 12-18 months. Tab. itraconazole 200 mg (BD) for a month.

CONCLUSION(S)

Presence of NTM in respiratory specimens in patients with underlying lung disease is not to be ignored clinically even in immunocompetent patients. Patients diagnosed with NTM should be screened for *Aspergillus* co-infection by IgM, IgG antibodies and culture. Respiratory panel including *Aspergillus* species, *Mycobacterium* Other Than Tuberculosis (MOTT) should be made mandatory for immunocompromised patients to lessen the delay in diagnosis and treatment.

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