Treatment of Slowly Growing Mycobacteria

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KEYWORDS

• Nontuberculous mycobacteria • Mycobacterial disease • MAC • *Mycobacterium avium* complex • *M avium* • Bronchiectasis • NTM • Slow-growing mycobacteria

KEY POINTS

- The treatment of slow-growing mycobacteria requires a multidrug regimen and a long course of therapy, typically 12 to 18 months.
- The only drugs for which in vitro susceptibilities correlate with an in vivo response in MAC lung disease are macrolides and amikacin.
- Patients with macrolide-resistant MAC and patients who do not respond to standard therapy require early referral and treatment at a specialized center.
- Inhaled amikacin may provide an adjunct therapy for the treatment of MAC lung disease, but adequate companion drugs are necessary to prevent the emergence of amikacin resistance.

INTRODUCTION

Historically, mycobacteria that form colonies visible to the naked eye in more than 7 days on subculture media are termed slow growers. Slowly growing nontuberculous mycobacterial (NTM) species include *Mycobacterium avium* complex (MAC) (*M intracellulare*, *M avium*, *M chimaera*), *M kansasii*, *M haemophilum*, *M marinum*, and *M ulcerans.* Less commonly encountered pathogens in the United States include *M scrofulaceum*, *M malmoense*, *M simiae*, *M szulgai*, *M terrae complex*, and *M xenopi*, although the latter is a significant source of lung disease in Canada, Northern Europe, and other parts of the world. Slowly growing NTM species were the first NTM to be recognized as causing chronic lung disease.

PATIENT EVALUATION OVERVIEW

Slowly growing NTM lung disease, especially caused by MAC, is broadly associated with 2 distinct radiographic forms of disease. The first to be described involves upper lobe fibrocavitary densities resembling pulmonary tuberculosis and occurs primarily in men with underlying obstructive lung disease (Fig. 1A). The second radiographic manifestation involves nodules and bronchiectasis and occurs primarily in women without underlying pulmonary disease other than bronchiectasis and in the United States is the most common presentation of the most common slowly growing NTM pathogen, MAC (see Fig. 1B). Although MAC is the best described NTM pathogen with this radiographic dichotomy, it has also been described with most other slowly growing NTM pathogens.[1]

Kim and colleagues[2] from the National Institutes of Health (NIH) reported 63 patients (95% female) with NTM lung disease and a characteristic body habitus including lower body weight and significantly greater height than matched controls. These patients also had higher rates of scoliosis (51%), pectus excavatum (11%), and mitral valve prolapse (9%) compared with matched controls. No cytokine pathway abnormalities or cell-mediated dysfunction were found in these patients. In a recent similar report, investigators

Disclosure: Dr. Philley served on an advisory board for Insmed Pharmaceuticals in 2014.
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Clin Chest Med 36 (2015) 79–90
http://dx.doi.org/10.1016/j.ccm.2014.10.005

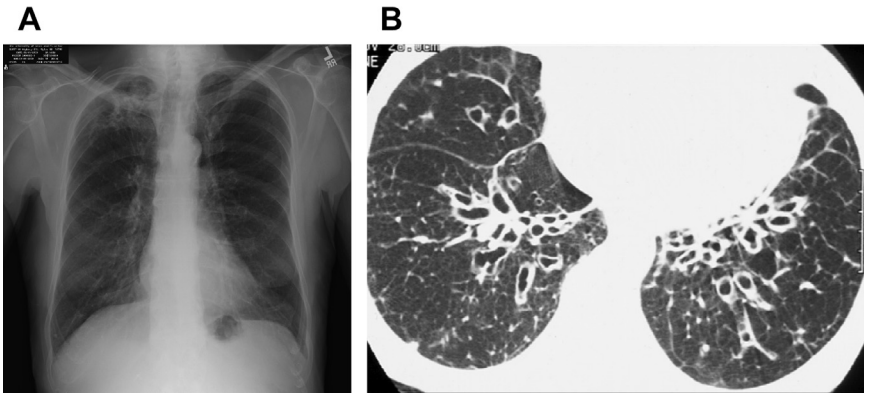

Fig. 1. (*A*) A 79-year-old man with greater than 100 pack year history of cigarette smoking and severe emphysema, who presented with worsening cough, fatigue, and weight loss. Posteroanterior chest radiograph shows right upper lobe cavitary lesion, with dense surrounding inflammatory changes. Sputum cultures were positive for *M xenopi* on multiple specimens. The patient was successfully treated with azithromycin, ethambutol, and rifampin. (*B*) A 68-year-old woman with bronchiectasis by chest computed tomography.

from National Jewish Health[3] again noted the characteristic body habitus of female patients with MAC lung disease but, in contrast to the NIH study, found decreased cytokine (interferon γ and interleukin 10) response of stimulated peripheral blood monocytes from patients with MAC compared with controls.

The NIH study also found a higher incidence of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene mutations (36%) compared with a matched control population, although there was no consistent correlation between sweat chloride concentrations and CFTR variants. It has also been noted in Japan[4] that patients with pulmonary NTM disease have CFTR gene mutations more frequently than in the general population. In a recent study,[5] patients heterozygous for CFTR mutations were found to have abnormal nasal potential differences compared with controls, suggesting a subtle mucosal ion transport abnormality and a possible pathophysiologic pathway for developing bronchiectasis. However, there is no clear connection between single CFTR mutations and the characteristic body habitus described earlier or a clearly delineated mechanism through which a single CFTR mutation might cause bronchiectasis.

The consensus among most NTM lung disease experts is that bronchiectasis precedes and predisposes to NTM infection similar to what is observed in patients with CF.[6,7] However, some patients with NTM lung disease associated with nodules and bronchiectasis have nodular infiltrate, which may precede the development of cylindrical bronchiectasis. For these patients, therefore, NTM infection might be the cause of their bronchiectasis. In the absence of early and sensitive measures to detect bronchiectasis or an animal model of chronic NTM lung disease, this chicken and egg question is impossible to answer for many patients. Likely, there are many phenotypic pathways to the development of bronchiectasis with or without NTM lung disease. From a practical standpoint, patients with known bronchiectasis for any reason should be screened for NTM infection and should be considered for evaluation of genetic or hereditary causes of bronchiectasis.

Although the current research and public health emphasis in the United States is on NTM lung disease associated with nodules and bronchiectasis, it is important not to forget the fibrocavitary form of slowly growing NTM lung disease, which more closely resembles tuberculosis radiographically and clinically. *M avium* complex lung infection was initially recognized with this radiographic manifestation, and in some areas in the United States, it still accounts for much of the observed MAC lung disease. Other slowly growing respiratory NTM pathogens such as *M xenopi*, *M kansasii*, *M szulagi*, and *M malmoense* present more frequently with cavitary lung abnormalities than with nodules and bronchiectasis. In contrast to the United States, in some parts of the world, especially Western Europe, fibrocavitary NTM disease is more common overall than disease associated with nodules and bronchiectasis.[8,9] An important predisposing association for the development of cavitary NTM lung disease seems to be cigarette smoking.[10,11] In that regard, cavitary NTM lung disease is pathophysiologically distinct from nodular/bronchiectasic disease and should probably be considered another in a long list of cigarette smoking–related diseases. Although there are important pathophysiologic differences, both disease presentations seem to require the