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Review Article

Management of nontuberculous mycobacterial infection in the elderly

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ABSTRACT

The incidence of nontuberculous mycobacteria (NTM) has increased over the last decades. Elderly people are more susceptible to NTM and experience increased morbidities. NTM incidence is expected to rise due to an increasing elderly population at least up to 2050. Given the importance of NTM infection in the elderly, an increasing interest exists in studying NTM characteristics in the aged population. In this review, we summarize the characteristics of NTM infection among elderly patients. We focus on epidemiology, clinical presentation, and treatment options of NTM in this age group. We highlight the differences in the diagnosis and treatment between rapid and slow growing mycobacterial infections. The current recommendation for treatment of NTM is discussed. We debate if in vitro susceptibility testing has a role in the treatment of NTM. Drug–drug interaction between antibiotics used to treat NTM and other medications, particularly warfarin, is another important issue that we discuss. Finally, we review the prognosis of NTM disease in elderly patients.

1. Case report

A 70 year-old woman was referred to our Bronchiectasis Clinic for chronic cough. Her past medical history was significant for 30pack-year smoking and measles without pneumonia in childhood. She stated that for the last 9 months she had a productive cough and chest pain. The cough had gradually progressed along with yellow, brown or blood tinged sputum. She first noticed hemoptysis 8 months prior and the last hemoptysis episode was a few weeks ago, but never expectorated gross blood. She received a course of levofloxacin with some temporary improvement in symptoms.

The chest pain was localized to midsternum and described as stabbing, burning, and heavy pressure feeling. It improved with sleep and worsened by singing, smoke exposure, coughing, eating oily food, sitting and standing. While she noted awakening due to coughing, she did not note a relation to position.

She had no dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fever, chills, night sweats, weight loss as well as history of environmental or drug allergies asthma, tuberculosis (TB), diabetes, gastroesophageal reflux disease, seizure, HIV risks (including drugs, multiple sexual partners and transfusions) and exposure to TB patient, silica or significant asbestos. She worked in office jobs in the past.

Past medical history included measles, a throat abscess at age 12, tonsillectomy at age 13 and hemorrhagic gastritis 8 years ago. She had kidney stones that were removed.

Family history was significant for emphysema and chronic bronchitis. She was taking low dose aspirin for heart disease prevention and naproxen for joints pain.

Review of systems uncovered lightheadedness with palpitation, early satiety, and posterior neck pain.

On physical examination, the patient was a well-appearing, white woman in no distress. Her weight was 70.9 kg. Her vital signs included pulse 105/min, blood pressure 122/78 mmHg, and temperature 36.9 °C. Her oxygen saturation was 94% at room. The lungs had crackles at the bases but these improved with repeated breathing. She also had scant wheezing in the right anterior lower chest. The point of maximum impulse of the heart was not palpated. S1 and S2 were normal. She had a midsystolic click and I–II/VI systolic murmur. There was no gallop. The rest of the physical examination was within normal range of limits.

The chest images showed many nodules, right middle lobe bronchiectasis, upper and lower lung circular opacities, suggesting bronchial and bronchiolar cuffing and lucencies that indicated cystic

Abbreviations: TB, tuberculosis; Ig, immunoglobulins; NTM, nontuberculous mycobacteria; US, United States; MAC, *Mycobacterium avium* complex; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; HLA, human leukocyte antigen; HP, hypersensitivity pneumonitis; ATS, American Thoracic Society; IDSA, Infectious Diseases Society of America; IGRA, IFN-γ release assay; FISH, fluorescence in situ hybridization; MTB, *M. tuberculosis*; SGM, slow growing mycobacteria; RGM, rapidly growing mycobacteria; HPLC, high-performance liquid chromatography; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; CLSI, Clinical and Laboratory Standards Institute; CYP, Cytochrome P-450; INR, international normalized ratio.

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bronchiectasis. She also had mild scoliosis (Images 1 and 2). Laboratory tests showed normal CBC and differentiation, total serum levels of immunoglobulins (Ig) E, A and G, blood chemistries and lipid profile. ECG was within normal limits.

Three sequential sputum specimens were sent for AFB smear, culture and drug susceptibility testing. Two days later, AFB smears reported positive and PCR test showed negative for *Mycobacterium tuberculosis* complex. From two sputum cultures *Mycobacterium avium* was isolated later. In vitro antibiotics susceptibility testing showed the *M. avium* isolate was sensitive to clarithromycin, ciprofloxacin, moxifloxacin, rifabutin, rifamycin, clofazimine and ethambutol, but resistant to cycloserine and amikacin, and intermediate to streptomycin and kanamycin.

Given clinical symptoms, chest x-ray and CT-scan results, and two positive sputum specimens for *M. avium*, pulmonary nontuberculous mycobacteria (NTM) was diagnosed and treatment was started with clarithromycin 500 mg twice per day, rifampicin 600 mg once a day and ethambutol 1200 mg once a day. Her cough and chest pain were gradually improved. The sputum cultures for AFB were obtained monthly until sputum conversion. Her sputum cultures converted negative within 4 months after initiating antibiotics therapy. She was categorized as cured when she completed 12 months treatment after sputum conversion. She was closely observed and no evidence of relapse was detected up to 2 years of follow up.

2. Introduction

Nontuberculous mycobacteria have been recognized as human pathogens since the 1950s, and to date, over 150 species of *Mycobacterium* have been identified [1–3]. Table 1 shows the most common NTM that cause infection in the elderly. They represent a diverse group of environmental organisms that can be isolated from water sources, soil, animals, and food [4,5]. Human NTM infection is mainly acquired from environmental exposures [6,7], although potential human-to-human transmission was recently suggested [8]. The NTM incidence has been increasing in the last decades. HIV was responsible for this increase from the 1980s to 1990s. Afterward, the increase has mainly been in women without any of the classic risk factors. Although the exact cause is unclear, it may be a result of the improved methods of NTM detection, as well as growth of the elderly population [9–12].

Similar to the rest of the world, both the United States (US) and Europe are facing with an aging population and it is estimated that the number of people aged 65 and older in the US will increase to 88.5 million in 2050. It is almost twice the elderly population in 2010 (40.2 million) [13,14].

Elderly people are more susceptible to NTM and most likely to need health and long-term caring services. The average age for NTM infection is reported between 50 and 70 years old [15]. It was shown that age is an important prognostic factor for NTM disease [16]. Elderly HIV population is another concern [17,18]. Given that approximately 34 million people live with HIV infection in the world (2,300,000 of those in Europe) [19], HIV associated NTM will become an important health concern in the coming years.

Despite the importance of NTM infection in the elderly, there is limited information on the characteristics of diseases caused by these pathogens. The aim of this study was to briefly review the epidemiology and clinical characteristics of NTM diseases among the elderly patients.

3. Methods

A literature search was performed for articles published between 2000 and 2013 using the search terms 'nontuberculous mycobacteria' and 'elderly', 'epidemiology', 'treatment', 'symptoms', 'prevention' and 'diagnosis'. PubMed, Cinahl, Embase and the Cochrane Library were reviewed. Titles of interest were further reviewed by abstract. Reference lists of relevant studies were hand-searched for additional studies.

Studies included in this review met the following criteria:

- Study populations included patients with NTM.
- Articles were full reports, case reports or reviews.
- Articles were in English.
- Articles were published in peer-reviewed journals.

4. What is the prevalence of NTM among the elderly?

Although the incidence of pulmonary infection by NTM has been noted to be increasing, a formal epidemiological evaluation of this disease has been deficient until recently [20]. According to a laboratory assessment from 1993 to 1996 performed by the Centers for Disease Control and Prevention, the rate of positive NTM cultures was 7.5–8.2 cases per 100,000 persons. However, a recent survey showed a positive culture rate of 17.7 per 100,000 in non-HIV patients in the US [21–23]. Moreover, the rate of pulmonary disease with *Mycobacterium avium* complex (MAC) has been reported to be 0.2 cases per 100,000 in

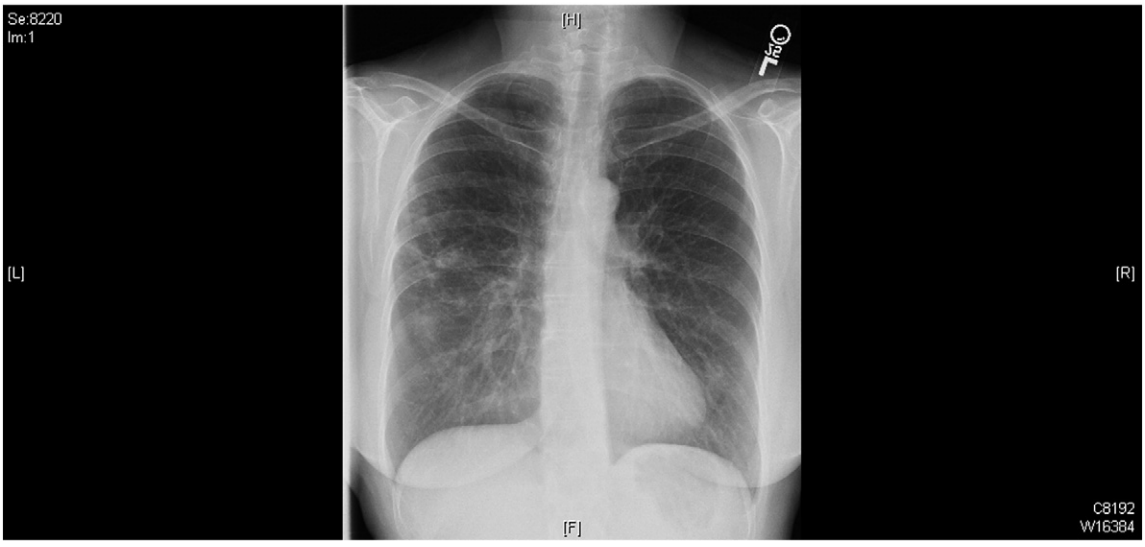

Image 1. The chest X-ray shows diffuse interstitial fibrotic-type opacities throughout both lungs. There are ill-defined somewhat nodular appearing densities with a hint of cavitation in them on the right side, particularly in the apical segment of the lower lobe. Mild scoliosis is notable.