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Review

Gender susceptibility to mycobacterial infections in patients with non-CF bronchiectasis



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ABSTRACT

Non-tuberculous mycobacteria (NTM) are environmental microbes that cause a variety of diseases both in immunocompromised and immunocompetent patients. Epidemiologic data indicate that there has been a global rise in the incidence of NTM infections. It has also been noted that NTM infections have a predilection to occur in postmenopausal women. In a recent study, it was demonstrated that in patients with non-CF bronchiectasis the probability of NTM isolation was significantly higher in elderly female patients and in those with a low body mass index. However, the mechanisms of causality of these gender differences and morpho-phenotypes remain enigmatic. The present study reviews the data and plausible mechanisms which might provide clues to this gender susceptibility and morpho-phenotypes of patients with bronchiectasis and NTM.

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Introduction

Nontuberculous mycobacteria (NTM) are environmental microbes that cause a variety of diseases, including chronic lung infections. NTM are normal inhabitants of soil and drinking water and hence are typically acquired from these sources. Similar to TB, NTM can infect any organ system. However, pulmonary infections, lymphadenitis and skin and soft tissue infections are the most common. Epidemiologic data suggest that there has been a rise in the incidence and prevalence of NTM infections and importantly NTM-related death numbers over the past decade [1]. Some studies suggest that the incidence of NTM is as high as 15.5 cases per 100,000 in persons over 50 years of age in the United States [2–4]. This increase has been attributed to improvements in investigative methodologies such as 16S rDNA gene sequencing to detect the presence of mycobacteria and awareness of the importance of NTM species as human pathogens [5,6]. Several studies have attempted to define the phenotypic characteristics of patients with NTM. Immunocompromised patients are particularly vulnerable and develop disseminated disease. Other known risk factors include cystic fibrosis, chronic obstructive pulmonary disease (COPD), silicosis, and alpha-1 antitrypsin deficiency [7–12]. Recent studies have also found an association between non-CF bronchiectasis and non-tuberculous mycobacterial infections [13]. Furthermore, studies suggest that this association is seen more often in post-menopausal women.

The association of non-CF bronchiectasis and NTM has been well described; however, the sequential causality has been debated and remains to be investigated. In some patients, bronchiectasis precedes the development of NTM similar to that seen in patients with cystic fibrosis. Nonetheless this association is increasingly recognized in tall thin post-menopausal women. The mechanisms which contribute to the predisposition of women to developing mycobacterial infections remain to be defined.

Non-CF bronchiectasis and mycobacterial infections

Although the association of non-CF bronchiectasis and NTM infections has been described regardless of the sequence of occurrence, there is limited information about the characteristics of the dual diseases of NTM and non-CF bronchiectasis. In a recent study, a cohort of patients with adult-onset bronchiectasis was evaluated to determine the prevalence of NTM in this group. One hundred and eighty-two patients diagnosed with non-CF bronchiectasis were included in this study. NTM was isolated from sputum or bronchoalveolar lavage (BAL) of 68 (37%) patients. *Mycobacterium avium complex* (MAC) was isolated from 81% of patients, *Mycobacterium chelonae* from 7%, *Mycobacterium kansasii* from 3% and other NTM from 9% of patients. The diagnosis of bronchiectasis and the isolation of NTM was significantly higher in female patients and those with low body mass indexes as confirmed by logistic regression analysis [13].

A study from Japan by Tanaka et al. found a strong association between nodular and bronchiectatic changes on

chest CT-scan and the isolation of mycobacteria in sputum or BAL (50% of patients). Interestingly, in their study they found a female predominance of almost 84% with association of mycobacterial disease and bronchiectasis (11 out of the 13). This extreme predominance may be related to the small sample size and may not be truly reflective of this association; it nonetheless does suggest an increased predilection for female patients [14]. A study published by Wickremasinghe et al. from the United Kingdom showed an association with NTM in 2% of patients with existing bronchiectasis [15]. However, of note, not all patients in their study had routine diagnostic tests for NTM from sputum and BAL. Therefore, it is possible that patients with NTM might have been missed in their study.

Marras et al. defined the clinical phenotypes of patients with mycobacterial infections in Toronto, Ontario and found that 62% of patients with mycobacterial infection had bronchiectasis with associated centrilobular nodules. It was not discerned whether bronchiectasis preceded infection with NTM. However, in those patients who had NTM and nodular bronchiectasis, they found a predominance of female patients (74%), whereas patients who had fibrocavitary disease and NTM were more likely to be male (77%). This study again suggests a high occurrence of NTM and bronchiectasis in women [16]. Together these studies suggest an association of NTM and bronchiectasis and that this association is seen more often in women.

Gender preponderance in mycobacterial infections

As discussed above, the incidence of NTM is increasing and several clinical and epidemiologic studies both from the US and other countries have defined the demographics of patients with NTM [17,18]. In general, most studies have found a female preponderance of NTM. Prevots et al. conducted a large population-based estimate of trends in NTM in the US using American Thoracic Society (ATS) microbiologic criteria. Their data was collected between 2004 and 2006 and showed that NTM had surpassed TB in the US with an increasing prevalence. They found that the prevalence of NTM was 1.1–1.6-fold higher among women relative to men across the different sites in the US [2]. In a single site study in Virginia, Satyanarayan et al. sought to describe the epidemiology of mycobacterial infections from 2001 til 2009. They found that most of the patients were above the age of 60; however, the sex distribution was equal in patients with NTM (50%) [19].

In a large population-based study in Europe conducted by NTM-NET collaborative group, an increasing incidence of NTM with a gender shift was shown with preponderance in female patients [20]. Studies from New Zealand and Australia have also shown a similar increase in NTM cases with a gender shift from middle-aged smoking men to older non-smoking women [21,22]. They also noted that the increased susceptibility in women was related to the body habitus of being tall and thin. Interestingly, a nationwide population study published from Denmark did not show a rise in the incidence of NTM over a 12-year period; however, they

showed that NTM colonization and disease have a poor prognosis. The negative prognostic factors included a high level of comorbidity, advanced age, male sex, and infection with *Mycobacterium xenopi* [23].

In a study from the National Institutes of Health which enrolled 63 patients with NTM showed that patients with pulmonary NTM had a characteristic morpho-phenotype. They found that these patients were taller and leaner than control subjects with high rates of scoliosis, pectus excavatum, mitral valve prolapse and cystic fibrosis transmembrane conductance regulator (CFTR) mutations [24]. A more recent study by Kartalija et al. investigated the morpho-types of patients with pulmonary NTM and measured adipokines and cytokines in these patients. They found that patients with pulmonary NTM had a distinct body phenotype with increased scoliosis and pectus excavatum. In addition, they found that these patients have lower levels of IFN- γ and IL-10 with altered adipokine and leptin levels [25]. In a recent retrospective study, Lee et al. reviewed patients with pulmonary NTM between 2005 and 2012. In their study a total of 148 patients with NTM lung disease and 142 age- and sex-matched controls were enrolled. They found that 60.8% of patients were women, and patients with both localized disease and extensive NTM disease had less subcutaneous fat compared with the control group [26].

Together these data suggest that there is compelling evidence for the predisposition of older women with slender body habitus to NTM. Therefore, the question arises if this is in some way related to altered sex hormones. In an experimental model, Tsuyuguchi et al. infected ovariectomized mice with intra-tracheal MAC. They found that the bacterial burden was significantly higher in ovariectomized mice compared with the sham control. Furthermore, treatment of ovariectomized mice with exogenous estrogen enhanced the bacterial clearance [27]. In a study of 35 patients, Danley et al. measured the levels of dehydroepiandrosterone-sulfate (DHEA-S), estrone, and ultrasensitive estradiol blood samples. They found that women with MAC infection had lower DHEA-S levels, but not lower estrogen levels, compared with control subjects. There was no relationship between BMI and hormone levels in their study population. Although the study makes an interesting observation, the small sample size makes it difficult to make definitive conclusions [28].

The above studies suggest a role for estrogen in immune response to NTM. However, the mechanisms by which estrogen enhances host defense to NTM remains to be defined. In an excellent manuscript published by Chan and Iseman, the contribution of sex hormones and the mechanism by which they might modulate the NTM response was reviewed. They hypothesize that hormones such as Luteinizing hormone (LH) and estrogen may contribute to altered leptin and adiponectin levels that in turn may modulate the host response in terms of cytokine and chemokine expression (IL-10, TGF- β). Alternatively, it is plausible that altered leptin and adiponectin levels in thin individuals may contribute to the predisposition to NTM infections [29]. The phenotype of bony abnormalities and association with mitral valve prolapse has been hypothesized to abnormal fibrillin levels that in turn

can modulate TGF- β expression, although experimental data to support these findings needs further work.

A recent study from Taiwan by Hsieh et al. found Matrix metalloproteinase-1 (MMP1) polymorphisms among patients with non-CF bronchiectasis [30]. Their study suggests that bronchiectasis patients with MMP-1(-1607G) polymorphism may be more vulnerable to permanent lung fibrosis and/or airway destruction due to the enhanced MMP-1 and TGF- β 1 activity. Another study by Maisi et al. showed that patients with bronchiectasis had elevated levels of soluble activated and autocatalyzed Membrane type 1 metalloprotease (MT1-MMP) species, as well as activated forms of MMP-2 in induced sputum and bronchoalveolar lavage fluid [31]. Karakoc et al. measured the levels of MMP-9 from children with CF and non-CF bronchiectasis from exhaled breath condensates [32]. They showed that patients with CF and non-CF bronchiectasis had increased levels of MMP-9 in exhaled breath condensates. There are studies that have hypothesized that abnormal production of MMPs may contribute to the tissue destruction seen in subjects infected with *M. tuberculosis*, although similar data from NTM patients is scant.

In a recent study, Sakamoto et al. showed that mycobacterial trehalose dimycolate reprograms macrophage global gene expression and activates matrix metalloproteinases. Of note, mycobacterial trehalose is a major glycolipid component of all mycobacteria and therefore similar to *M. tuberculosis* expression of MMPs by NTM and may contribute to the pathogenesis of NTM lung disease [33]. Together, these data suggest that the dual presence of bronchiectasis and NTM may be related to dysregulation or overproduction of MMPs. It is also possible that the predilection might be related to polymorphisms in genes regulating the production of MMPs [33].

Summary and conclusions

Evidence shows that the incidence of NTM is increasing worldwide with MAC being the most frequent cause. This may be the result of improved diagnostics and increased recognition of the importance of NTM as a causality of lung disease. The conditions that predispose to NTM have included chronic lung diseases, such as cystic fibrosis, COPD, and alpha-1 antitrypsin deficiency; however, association with bronchiectasis continues to remain enigmatic. Whether NTM invade preexisting bronchiectasis or lead to de novo initiation of bronchiectasis is debatable. Nonetheless, epidemiologic data have repeatedly suggested that NTM has a predilection to affect thin, elderly (post-menopausal) women without underlying lung disease for unclear reasons. As in this study many of these women also develop bronchiectasis. Several plausible hypotheses have been generated to explain these differences, including the role of sex hormones and mediators, such as leptin and adiponectin, which modulate key cytokines such as TGF- β . Whether sex hormones truly contribute to these gender differences remains to be established, and the mechanisms are not understood. Fibrillins and matrix metalloproteinases are other potential mediators that might contribute to the pathogenesis of dual disease with NTM and bronchiectasis. Further

studies in experimental models are sorely needed to elucidate the contribution of hormones, mediators and nutritional status in the immuno-pathogenesis of NTM infections.

Authors' contribution

Conception, review literature, design, and modeling for review writing of the paper were done by M.M. and R.T.S. Writing the paper or substantial involvement in its revision before submission was by M.M. and R.T.S.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper. Mehdi Mirsaeidi was supported by NIH Grant 5 T32 HL 82547-7.

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