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ORIGINAL ARTICLE

High recurrence rate of lymphadenitis due to nontuberculous mycobacteria and its association with concurrent *Salmonella* infection in Taiwan

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Background: The objective of this study is to investigate the clinical characteristics of lymphadenitis due to nontuberculous mycobacteria (NTM) in Taiwan.
Methods: We retrospectively reviewed the medical records of all patients who presented to the National Taiwan University Hospital with culture-positive NTM lymphadenitis during the period 2000—2010. Patients with concurrent extranodal involvement were excluded.
Results: From 2000 to 2010, 15 patients with lymphadenitis caused by nontuberculous mycobacteria were identified. Most patients (80%, $n = 12$) were infected with rapidly growing mycobacteria. *Mycobacterium abscessus* was the most common infective species ($n = 8$). Recurrence of infection involving multiple organs occurred 2—7 years after the completion of treatment in 11 (73%) patients. Five (33.3%) patients had concurrent *Salmonella* infections (4 patients with bacteremia and 1 patient with empyema thoracis) during the course of the disease.
Conclusion: In Taiwanese patients, we found a high recurrence rate of NTM lymphadenitis that was closely associated with *Salmonella* infections. We also noted that the clinical and

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epidemiological manifestations of NTM lymphadenitis in Taiwan differed from their manifestations in western countries.

Introduction

Nontuberculous mycobacteria are environmental opportunistic pathogens. Nontuberculous mycobacteria (NTM) cause a wide variety of diseases, including disseminated infections, skin and soft tissue infections, pulmonary infections, central nervous system infections, genitourinary tract infections, and lymphadenitis.[1–10] In developing countries, *Mycobacterium tuberculosis* is the most common mycobacterium that causes lymphadenitis. In developed countries, however, NTM causes up to 95% of cases of mycobacterial cervicofacial lymphadenitis.[11] Cervicofacial lymphadenitis caused by NTM normally occurs in children during the first 5 years of life and the *Mycobacterium avium* complex is the most frequently isolated species.[11] However, the distribution of the NTM species is not uniform and appears to be geographically or environmentally dependent.[12,13]

Materials and methods

In this study, we retrospectively reviewed the medical records of all patients who presented to the National Taiwan University Hospital from 2000 to 2010 with culture-positive NTM lymphadenitis. Patients with concurrent extranodal involvement (i.e., disseminated infection) were excluded. Disseminated infections caused by NTM have been previously reported.[14] One patient reported in this study was included in our previous report.[15]

Formalin-fixed paraffin-embedded tissue blocks of the lymph node biopsy specimens were retrieved from the department of pathology. Re-cut histological sections with hematoxylin and eosin staining were reviewed and Ziehl-Neelsen acid-fast staining was performed. The recommended guidelines were followed for preparing lymph nodes and other clinical specimens for cultures of mycobacteria.[16] NTM isolates were identified to the species level by using conventional biochemical methods and 16S rRNA gene (1464 bp) sequencing, as previously described.[17]

Results

Fifteen patients with culture-positive NTM lymphadenitis were treated at the hospital (Table 1). The patients comprised 14 (93%) adults and one (7%) child and their mean age was 51.8 years. Twelve patients had lymphadenitis caused by rapidly growing mycobacteria (RGM) such as *M. abscessus* ($n = 8$), *M. chelonae* ($n = 2$), *M. fortuitum* ($n = 2$), and three patients had lymphadenitis caused by slowly growing mycobacteria such as *M. kansasii* ($n = 2$) and the *M. avium* complex ($n = 1$). Thirteen patients (87%) presented with multiple lymphadenitis (i.e., involving multiple nodes, as indicated by computed tomography) during the disease course and two patients presented with localized lymphadenitis [involving a single node in the carina ($n = 1$) and neck ($n = 1$)]. Cervical lymph nodes were involved in 13 (87%) patients. Six (40%) patients had a fever as the initial presentation. Seven (47%) patients had underlying medical diseases that, in five of the patients, may have resulted in a clinically immunodeficient status: two patients had chronic myelogenous leukemia, one patient had liver cirrhosis, one patient had Sjögren's syndrome, and one patient had polyneuropathy. All five patients presented with multiple lymphadenitis.

During the course of the disease, five patients had concurrent *Salmonella* infections (four patients with bacteremia and one with empyema) thoracis due to non-typhi *Salmonella*. Four patients with recurrent NTM lymphadenitis had *Salmonella* infections during the first episode of NTM disease. None of the patients with localized NTM lymphadenitis had an underlying disease or *Salmonella* infection. The five patients with *Salmonella* infection received treatment with third-generation cephalosporins (e.g., cefotaxime or ceftriaxone). They all recovered.

Conventional antituberculous therapy (e.g., isoniazid, ethambutol, rifampin, and pyrazinamide) was the initial treatment in eight patients. After culture results were available, a clarithromycin- or azithromycin-containing regimen was administered from 4 weeks to 2 years in all but two patients (Patients 1 and 3). The two patients who did not receive the clarithromycin- or azithromycin-containing regimen (isoniazid + rifampin or isoniazid + rifampin + ethambutol, respectively) had localized NTM lymphadenitis and were treated with the surgical removal of the affected nodes and with antimicrobial agents. Lymphadenitis resolved after surgery in both patients.

Recurrent infection resulting from the same organisms occurred 2–7 years after the cessation of treatment in 11 (73%) patients. All recurrent events occurred in 11 (85%) patients with multiple lymphadenitis. Among the patients with recurrent disease, the lung was the most common site of infection ($n = 6$; 55%), followed by skin (46%; $n = 5$), perinodal soft tissue (46%; $n = 5$), bone and joints (18%; $n = 2$), and spleen (9%; $n = 1$).

A histopathologic examination revealed granulomatous inflammation with microabscess formation in 10 (67%) of the 15 lymph node biopsy specimens, and five (33%) of the specimens showed evidence of caseating granuloma, which is characteristic of tuberculosis. Acid-fast bacilli were identified in six (40%) of the 15 tissue specimens (Table 1).

Discussion

There were several important findings in our study that differed from previous reports. First, the high prevalence of