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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

Table 1 Clinicopathological and microbiological characteristics of 15 patients with lymphadenitis caused by nontuberculous mycobacteria

Patient no. (age/sex)	Underlying medical condition	Site of lymphadenitis/ fever	Concurrent *Salmonella* infections/*Salmonella* species	Recurrence (years after completion of treatment)/ site of involvement	*Mycobacterium* spp.	Treatment regimen (duration)/resolution of lymphadenitis	Histology/detection of acid-fast bacilli
1. 61/M	Nil	Carina (single node)/no	No	No	*M. abscessus*	Isoniazid + rifampin (8 months)/yes	Caseating granuloma/−
2. 7/M	Nil	Neck (single node)/no	No	No	*M. fortuitum*	Clarithromycin (4 months)/yes	Granuloma, microabscess/−
3. 67/M	Hypothyroidism	Neck (multiple nodes), abdomen/yes	Bacteremia/ *Salmonella* O9 (group D1)	Yes (7)/peri-nodal soft tissue, lung, joint, peritoneum	*M. kansasii*	Isoniazid + ethambutol + rifampin (18 months)/yes	Suppurative granuloma/+
4. 57/F	Nil	Neck (multiple nodes), axilla, inguinal /yes	Empyema thoracis/ *Salmonella* O9 (group D1)	No	*M. chelonae*	Doxycycline + azithromycin+, trimethoprim-sulfamethoxazole (1 year)/yes	Granuloma, microabscess/−
5. 79/M	Nil	Neck (multiple nodes), axilla/no	No	Yes (8)/peri-nodal soft tissue, multiple skin lesions	*M. abscessus*	Clarithromycin (2 months)/yes	Granuloma, microabscess/+
6. 68/M	Liver cirrhosis	Neck (multiple nodes)/yes	No	No	*M. chelonae*	Doxycycline + clarithromycin (4 months)/yes	Granuloma, microabscess/−
7. 34/F	Nil	Neck (multiple nodes)/no	No	Yes (4)/lung, bone, multiple skin lesions	*M. fortuitum*	Clarithromycin + ciprofloxacin (3 months)/yes	Suppurative granuloma/−
8. 71/F	Nil	Neck (multiple nodes) /no	Bacteremia/ *S. enteritidis* serotype Typhymurium	Yes (5)/spleen	*M. abscessus*	Levofloxacin, rifabutin, ethambutol, clarithromycin (1 year)/yes	Caseating granuloma/+
9. 54/M	Nil	Neck (multiple nodes)/yes	Bacteremia/ *Salmonella* O9 (group D1)	Yes (4)/lung, bone, multiple skin lesions	*M. avium*-complex	Ciprofloxacin + azithromycin + ethambutol + rifabutin (1 year)/yes	Granuloma, microabscess/+
10. 30/M	Chronic myeloid leukemia	Neck (multiple nodes), mediastinum/yes	No	Yes (3)/peri-nodal soft tissue, lung	*M. kansasii*	Clarithromycinl + moxifloxacin (8 months)/yes	Caseating granuloma/+
11. 57/M	Nil	Neck (multiple nodes), abdomen/no	No	Yes (4)/peri-nodal soft tissue	*M. abscessus*	Doxycycline + moxifloxacin + clarithromycin (8 months) and clarithromycin + moxifloxacin (2 years)/yes	Suppurative granuloma/+

(*continued on next page*)

Table 1 (*continued*)

Patient no. (age/sex)	Underlying medical condition	Site of lymphadenitis/fever	Concurrent *Salmonella* infections/*Salmonella* species	Recurrence (years after completion of treatment)/site of involvement	*Mycobacterium* spp.	Treatment regimen (duration)/resolution of lymphadenitis	Histology/detection of acid-fast bacilli
12. 65/F	Sjogren's syndrome	Neck (multiple nodes, inguinal)/yes	No	Yes (5)/lung	*M. abscessus*	Clarithromycin + doxycycline (7 months)/yes	Granuloma, microabscess/−
13. (29/M)	Polyneuropathy	Neck (multiple nodes)/no	Bacteremia/*S. paratyphi* A	Yes (2)/multiple skin lesions	*M. abscessus*	Clarithromycin (2 years)/yes	Caseating granuloma/−
14. (38/M)	Chronic myeloid leukemia , liver cirrhosis	Supraclavicular, mediastinum/no	No	Yes (2)/lung	*M. abscessus*	Doxycycline + clarithromycin (14 months)/yes	Caseating granuloma/−
15. (46/F)	Previous tuberculosis	Neck (multiple nodes), carina, axilla/no	No	Yes (4)/peri-nodal soft tissue, multiple skin lesions	*M. abscessus*	Imipenem + amikacin, ciprofloxacin + clarithromycin (4 weeks)/yes	Suppurative granuloma/−

NTM lymphadenitis and high recurrence rate in 93% of adult patients in this study has also been previously described.[15] Differences in the age of onset of NTM infection, particularly otitis media, have also been noted between patients in Taiwan and in patients in western countries.[18] The reasons for the late onset of NTM infection in Taiwan remains unknown, but it may be related to the nationwide administration of the bacillus Calmette-Guerin (BCG) vaccine. In a recent National Institutes of Health study of 141 patients with IL-12Rβ1 deficiency, patients with BCG vaccination had a later onset of a subsequent NTM infection, compared to patients who had not been vaccinated with BCG.[19] The BCG vaccination may have a protective role against subsequent NTM infection.[19] However, more studies on NTM lymphadenitis in countries with BCG vaccination are needed to clarify this issue. The high recurrence rate of NTM lymphadenitis in the current study may be related to inadequate antimicrobial therapy, lack of adequate surgical intervention to treat multiple lymph nodes, or an underlying immunodeficient status of the patients.

Second, NTM lymphadenitis in western countries usually presents as an isolated neck infection.[1,11] In our study, however, 13 patients presented with lymphadenitis involving multiple lymph nodes or localized lymphadenitis that eventually involved multiple nodes. In addition, most cases of NTM lymphadenitis in western countries occur in immunocompetent children without underlying disease.[1] In our study, five patients had an underlying disease such as chronic myelogenous leukemia, liver cirrhosis, Sjögren syndrome, or polyneuropathy, which may lead to immunodeficiency and secondary NTM infection. By contrast, adult-onset immunodeficiency may be a possible explanation for seemingly immunocompetent patients who develop disseminated NTM disease, as a recent study in Taiwan and Thailand indicates.[20]

Third, five patients in our study had concurrent infections because of non-typhi *Salmonella*, but only patient had underlying disease (e.g., polyneuropathy) that may have been associated with immunodeficiency. All five patients also had multiple NTM lymphadenitis. Therefore, there should be another cause that contributes to concurrent NTM and *Salmonella* infection in these patients. Further study focusing on T cell immunity in these patients may be helpful to clarify the issue because the mononuclear phagocyte/Th1 T cell pathway have been associated with NTM and *Salmonella* infection.[19]

Finally, *M. abscessus* was the most common NTM species isolated from the infected lymph nodes in our study. However, the *Mycobacterium avium* complex, rapidly growing mycobacteria, and *M. scrofulaceum* are the most common causative agents of NTM lymphadenitis in developed countries.[1,11] The high prevalence of *M. abscessus* infection in Taiwan has also been noted in other organs such as cornea, ear, skin, and lung.[15,17,18] The abundance of *M. abscessus* in the environment in Taiwan may explain this fact.[21,22]

All patients in our study received a biopsy or resection of the infected lymph nodes for pathological diagnosis. Microabscesses and ill-defined granulomas with occasional suppurative granuloma formation were the most common histological findings. However, five (33.3%) patients had caseating granuloma, which is characteristic of tuberculosis.

In summary, the clinical and epidemiological manifestations of NTM lymphadenitis in Taiwan differ from their manifestations in western countries. The high prevalence of recurrence and concurrent *Salmonella* infection among these patients warrant further investigation.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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