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Treatment patterns of pediatric nontuberculous mycobacterial (NTM) cervical lymphadenitis as reported by nationwide surveys of pediatric otolaryngology and infectious disease societies

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ABSTRACT

Objective: To describe physician diagnostic and therapeutic strategies for pediatric nontuberculous mycobacterial (NTM) lymphadenitis, a disease for which surgical excision is recommended.
Methods: We surveyed members of the Infectious Diseases Society of America Emerging Infections Network (EIN) and the American Society of Pediatric Otolaryngology (ASPO). We asked them to report clinical and microbiologic details of recent cases of NTM lymphadenitis seen in their practices.
Results: 200 physicians reported a total of 277 NTM lymphadenitis cases. Cervical lymph nodes (84%) were most frequently involved, and a majority of patients were non-Hispanic white (62%) males (54%) with median age 3.0 years. Tissue culture (61%) or polymerase chain reaction (12%) was utilized most frequently to confirm NTM etiology. In most (59%) cases, an etiologic organism was not identified. In cases, where an NTM organism isolate was identified, *Mycobacterium avium* complex ($n = 82$, 72%) was the most common. Surgical excision followed by adjunctive antibiotic therapy was favored in the majority (59%) of cases where a treatment method was reported. The use of surgical excision alone or antibiotic therapy alone was reported respectively in 24% and 17% of cases. Antibiotics were prescribed without diagnostic confirmation of infectious organisms in 28% of cases.
Conclusion: Pediatric otolaryngologists and infectious disease specialists frequently treat cervical lymphadenitis empirically as NTM disease without bacteriologic confirmation. Antibiotic therapy is frequently employed with or without surgical excision.

1. Introduction

Nontuberculous mycobacteria (NTM) are environmental organisms commonly found in municipal water systems and soil. NTM are a frequent cause of infectious lymphadentitis in healthy toddlers and young children. Over 125 species of NTM have been isolated worldwide, many of which are considered to be clinically significant [1–3]. Numerous reports have emerged in the last 14 years which suggest an overall rise in the number of cases of NTM infections seen in healthy children [4–6]. Despite these reports, the epidemiology and treatment of NTM lymphadenitis is not well documented.

In children, predominantly those ages 1–5 years [7], NTM infection often presents as chronic cervical lymphadenitis. Untreated, soft tissue and lymph node necrosis can lead to sinus tract formation, and severe disfiguration of the surrounding skin. Since these infections typically occur in the head and neck lymph nodes, near facial nerve branches, they can be clinically challenging to treat surgically.

Experts have debated the importance of antibiotic therapy in this setting, and previous studies supported surgical therapy as superior [8–10]. A recent randomized controlled trial also suggested the superiority of surgical excision over antibiotic therapy for the treatment of NTM cervical lymphadenitis [11], although it is unclear if this information has impacted treatment patterns among practitioners.

To better understand current clinical management of these infections, their bacteriology, and their frequency of occurrence, we surveyed two groups of pediatric specialists involved in the

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care of children with these infections: pediatric infectious disease specialists via the Infectious Diseases Society of America Emerging Infections Network (EIN), and also pediatric otolaryngology head and neck surgeons from the American Society of Pediatric Otolaryngology (ASPO).

2. Methods

In June 2007, we electronically surveyed all pediatric infectious disease specialists ($n = 214$) of the EIN. The EIN is a collection of 1/4 of the United States' infectious disease specialists who participate in regular communication via the Infectious Diseases Society of America (IDSA) supported list-serv. With a standardized survey, we asked physicians to report the number of NTM lymphadenitis cases seen in the last 6 months of their practices. For each case, we asked that they provide age, sex, race/ethnicity, region of lymphadenitis, organism(s) identified, and diagnostic and treatment methods practiced. In cases where physicians did not respond, we contacted them two additional times and collected responses until August 31, 2007.

We then created a similar survey using Survey Monkey™ (Portland, OR) that asked otolaryngology specialists to provide the same type of clinical information as listed above for all NTM lymphadenitis cases seen in their practices within the previous 12 months. A link to the survey was sent via e-mail to the 327 members of the ASPO, with responses canvassed from this group between February and April 2008. Similarly, we contacted non-responders two additional times during the survey period in order to improve survey response.

EIN data were entered into an Excel™ spreadsheet (Microsoft, Redmond, WA) and analyzed using CDC Epi Info (Version 3.2.4). We tabulated and analyzed ASPO data using the Survey Monkey™ spreadsheet. In the EIN network survey, we were able to enter age by month in children under 1 year old; whereas, within the ASPO survey, providers were able only to denote as "0–1 years" for any child less than 1 year old. For analytic purposes, we defined all ASPO ages listed as "0–1 years" as 6 months. Two-by-two comparisons of reported treatment patterns by ASPO and EIN clinicians were made using Mantel-Hansel odds ratios (OR) and Fischer p-values.

3. Results

3.1. EIN survey

Of the 214 EIN members contacted, 129 (60%) members responded, reporting a total of 111 cases (range, 0–15 cases per member) within the last 6 months. The majority of cases involved white, non-Hispanic ($n = 59$, 69%), males ($n = 47$, 57%). Median age was 3.0 years (range: 6 months to 16 years) (Table 1). The majority of reported NTM infections occurred within cervical lymph nodes (Table 2). Five percent ($n = 4$) occurred in inguinal regions and 7% ($n = 6$) in regions specified as "other." A tuberculin skin test (TST) was reportedly placed in 72 cases with 21% ($n = 15$) of cases reporting a "positive" result. Tissue culture was used in many cases to confirm the presence of NTM. Polymerase chain reaction (PCR) was employed in 5 cases. However, in 50 (45%) cases a presumptive diagnosis of NTM was made without microbiological or molecular confirmation (Table 2). *Mycobacterium avium* complex (MAC) was the most common causative agent, found in 45 (74%) of the 61 cases where an etiology was reported (Fig. 1). Other bacteria reported included rapidly growing mycobacteria (Fig. 1) and *Mycobacterium scrofulaceum*.

Of the 111 cases, physicians provided full treatment information for 85 (77%) cases. Twenty-seven (32%) of these were reportedly treated with surgical excision alone (Fig. 2). Physicians reported using antibiotic therapy alone ($n = 14$, 16%) or in combination with surgical excision ($n = 44$, 52%) in the remainder of cases (Fig. 2). Most EIN members (71%) estimated the incidence of NTM lymphadenitis had not changed in their practice when compared to "previous years," while equal numbers thought it was either increasing (15%), or decreasing (14%).

Table 1
Demographic Characteristics of NTM Cases as Reported by EIN and ASPO.

	EIN ($n = 111$) no. (%)	ASPO ($n = 166$) no. (%)
Median age (range), in years	3.0 (0.5–16)	3.0 (0.5–11)
Males	47 (57%)	38 (49%)
White, non-Hispanic	59 (69%)	41 (53%)
Hispanic White	15 (18%)	21 (27%)
Black	10 (12%)	11 (14%)
Asian	1 (1%)	2 (3%)
Native American	0	1 (1.5%)
Other	0	1 (1.5%)

Table 2
Clinical and Diagnostic Characteristics of NTM Cases Reported by EIN and ASPO Physicians.

	EIN ($n = 111$) no. (%)	ASPO ($n = 166$) no. (%)
Cervical or facial lymphadenitis	77/87 (89%)	74/75 (99%)
Use of tissue culture	72/111 (65%)	96/166 (58%)
Use of tissue PCR	5/111 (5%)	28/166 (17%)
Positive TST status	15/72 (21%)	19/63 (30%)

3.2. ASPO survey

Of the 327 ASPO members surveyed, 71 (22%) responded, reporting a total of 166 NTM lymphadenitis cases (range, 0–10 cases per member) within the previous 12 months. Cases were of median age 3.0 years (range: 6 months to 11 years). Thirty-eight (49%) of the reported cases were male, and 41 (53%) were white, non-Hispanic (Table 1).

Almost all ($n = 74$) NTM infections occurred within cervical or facial lymph nodes (Table 2). A TST was reportedly placed in 63 (38%) of the cases, with 19 (30%) yielding "positive" results. Although many cases were confirmed as NTM by tissue culture or PCR, the majority of NTM cases reported ($n = 113$, 68%) lacked a formal microbiological or molecular identification. MAC was identified as the causative agent in 37 (70%) of the 53 cases where an etiology was reported (Fig. 1).

Of the 166 cases, physicians provided full treatment information for 71 (43%) cases. Ten (14%) cases were reportedly treated with surgical excision alone, while antibiotics were reportedly used alone ($n = 12$, 17%), or in conjunction with surgical excision ($n = 49$, 69%) in the remaining cases (Fig. 2). As compared to the reported cases from EIN physicians, ASPO cases were less likely to rely upon surgical excision alone (OR 0.35, 95% CI 0.14–0.84; $p = 0.02$).

Similar to EIN physicians, however, most ASPO members (73%) estimated that the incidence of NTM lymphadenitis in their practice was not changing when compared to "previous years", while a small percentage felt it to be either increasing (10%), or decreasing (17%).

4. Discussion

We conducted a national survey among pediatric infectious disease and otolaryngology specialists within North America. The majority of participating clinicians reported seeing at least one or more recent cases of NTM lymphadenitis, and in more than half of

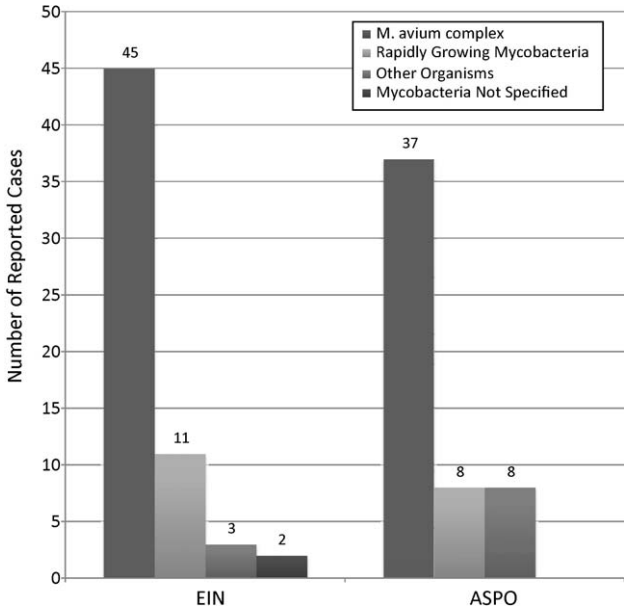

Fig. 1. Etiologic organisms of NTM lymphadenitis reported by pediatric otolaryngologists and pediatric infectious disease clinicians; American Society of Pediatric Otolaryngologists (ASPO), Emerging Infection Network (EIN).

the cases, reported using antibiotics either alone or in conjunction with surgical resection to treat these infections. Most cases occurred in young children and involved cervical or facial lymph nodes. The majority of these cases were caused by *M. avium* complex (MAC), although in a substantial proportion of cases the etiologic organism was not identified. Few practitioners reported using molecular diagnostic techniques in the clinical assessment of these patients.

NTM lymphadenitis frequently presents in children under 5 years old [6,7,12–14]. The reason for this is unclear, although a plausible explanation is that children of this age group are more likely to ingest NTM organisms through the oral exploration of objects that have been exposed to colonized soil or water. Such

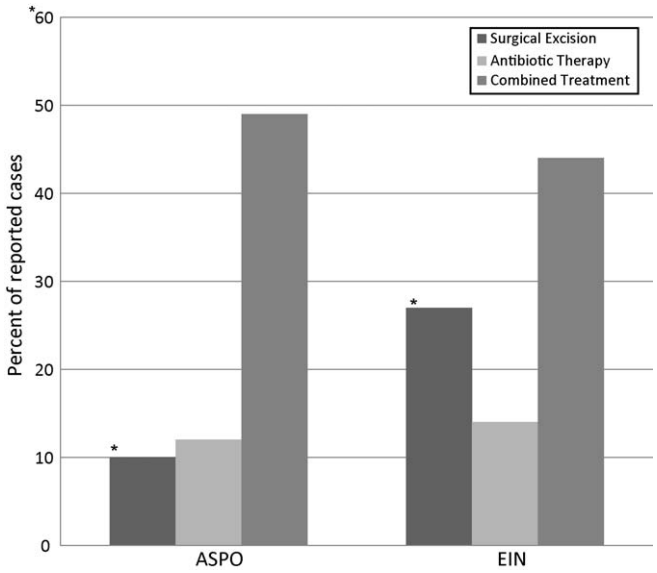

Fig. 2. Proportion of reported NTM lymphadenitis cases treated with surgical excision, antibiotic therapy, or combined antibiotic and surgical therapy, as reported by pediatric otolaryngologists and pediatric infectious disease clinicians; American Society of Pediatric Otolaryngologists (ASPO), Emerging Infection Network (EIN). *EIN physicians were more likely to report using surgical excision alone, $p < 0.05$ for comparison.

behavior may explain why the majority of pediatric NTM lymphadenitis cases involve the submandibular lymph nodes, as the infecting organisms may drain from openings in the teething child's gum line, into the oropharynx, ultimately finding their way to the cervical nodes [15]. Naïve immunity has also been indicated as a possible cause of this age trend, as children who are infected have probably had little or no prior exposure to mycobacteria [14].

Contrary to the findings of a recent clinical trial which suggested that surgical excision alone is the optimal form of treatment for NTM cervical lymphadenitis [11], we found that a majority of EIN and ASPO respondents favored a combination approach of surgical excision followed by antibiotic therapy. To date, there is little evidence suggesting that antibiotic therapy is necessary or adds to the benefits of surgical excision, and interestingly in our survey, infectious disease clinicians were less likely to use antibiotics in the treatment of their cases. Regardless, antibiotic therapy in lieu of surgery has been advocated in cases where the surgical risk of cranial nerve injury is thought too great, although Lindeboom and others investigators have shown that facial paralysis due to surgical excision is relatively unusual in the hands of experienced surgeons [11,12,14,16]. In cases where surgical excision is deemed of high risk, complete resolution of disease can be achieved with curettage of affected nodes instead of complete excision [17]. An observational-only approach has been advocated by some investigators, in that a recent study found a majority of untreated children self-healed within 6–9 months [18]. It is unclear whether this approach provides similar outcomes with regard to cosmesis, and the findings from this study suggest that further randomized controlled trials should be undertaken comparing observation with surgical excision.

In our series, it was common for both pediatric otolaryngologists and infectious diseases physicians to report using antibiotics empirically. A large number of the reported cases (59%) failed to show evidence of mycobacteria on culture or by molecular testing. This is, perhaps, not surprising in cases where surgical excision was not employed. Fine needle aspirates and wound swabs are poorly sensitive for documenting mycobacteria on culture [19]. Although we did not ask providers to provide details regarding biopsy procedures, many anecdotally reported using fine needle aspiration (FNA) to biopsy lymph nodes, or sending wound swabs from the operating room for acid-fast bacilli culture. Additionally, it is a well known phenomenon that many specimens taken in the operating room for culture are put into formalin for histopathological examination, a process that destroys mycobacteria or other organisms. Rather, open biopsy material should be placed within a sterile-saline filled container and sent for mycobacterial culture. Culture growth for many NTM is slow and can take up to 8 weeks for certain types of slow-growing species [20,21]. In cases where cultures are negative, sending biopsy material for PCR or other molecular testing could be considered, including samples that have been paraffin-embedded [22]. In cases where surgery is not possible and antibiotic therapy is employed, culture and antibiotic susceptibility results should be used to guide therapy. This is potentially important in those cases caused by rapidly growing mycobacteria (*Mycobacterium abscessus*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and others) where aside from macrolide susceptibility, the antibiotic profiles frequently differ from MAC and other slowly growing mycobacteria. Macrolide monotherapy can lead to the rapid development of macrolide resistance mediated by the erm gene present in *M. fortuitum* [23].

Other reasons to obtain adequate tissue for diagnosis include ruling out tuberculosis (TB). Approximately 10% of pediatric mycobacterial cervical lymphadenitis is due to tuberculosis in the United States. On the contrary, in adults with infectious causes of cervical lymphadenitis, TB is much more likely than NTM [1]. Children who are older, foreign born, or have a history of TB contact

are more likely to have disease due to TB, and clinicians should take steps to rule out such disease. Interestingly, a number of cases in our series were reported to have positive tuberculin skin test results during their work-up. Positive TST results could represent prior TB exposure or a false positive result due to NTM. The recently developed interferon-γ release assays (IGRAs) are likely a more useful diagnostic tool in the setting of cervical lymphadenitis, as these assays measure lymphocyte responses to antigens specific to *M. tuberculosis* and not present in strains used to make bacille-Calmette Guerin (BCG) vaccine, MAC, or most other clinically relevant NTM [24–26]. The limited data collected to date within pediatric populations suggest that IGRAs are reliable [27], although further longitudinal studies within this age group are necessary to establish the sensitivity of these tools in diagnosing TB in young children [28]. In patients where TB is suspected, tissue culture, PCR, TST, IGRA, chest radiograph, gastric aspirate, and other methodologies can be employed to investigate the possibility of active TB disease [29–31].

Our survey was limited in several important ways. First, while we achieved a reasonable response rate (60%) from the EIN, our ASPO survey garnered a lower response rate (22%), however one that was typical for their surveys (personal communication, Carol MacArthur, MD). Accordingly, it is unclear if the data provided by these 22% fully represent the experience of the entire membership of ASPO. We know of no reason why the responding physicians would have different treatment patterns than those who did not respond, but we cannot rule out this possibility. ASPO responses were similar in many aspects to those from the EIN physicians, although interestingly a lower percentage reported surgical excision alone in the management of their cases.

In summary, our national survey of pediatric infectious disease and otolaryngology specialists suggests that many pediatric NTM lymphadenitis cases are treated with antibiotics in this country despite a lack of evidence suggesting that antibiotic therapy improves outcomes over surgical excision alone. Further study is necessary to determine the role of antibiotics and observation in the therapy of this disease. Until then, physicians should make efforts to excise affected nodes, and to send tissue for culture and molecular testing in order to identify infecting organisms, and importantly, to rule out TB disease.

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