

First Canadian reports of cervical adenitis due to *Mycobacterium malmoense* and a 10-year review of nontuberculous mycobacterial adenitis

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The present report reviews a decade of experience with nontuberculous mycobacterial adenitis at a pediatric referral centre, noting that patients are often subjected to multiple ineffective antibiotic courses, and that delays in diagnosis and referral for appropriate therapy are common. Notable clinical features include a mean age of presentation of 3.4 years, a male-to-female ratio of 1:1.5 and a gradual onset of painless, unilateral cervical adenopathy. Fever was absent in most patients (77%), and the disease failed to respond to antistaphylococcal antibiotics. The mean time to correct diagnosis was longer than three months (15 weeks). The clinical features of the disease are highlighted and presented with a practical diagnostic approach to the child with subacute/chronic adenitis. New molecular diagnostic tools and emerging mycobacteria are discussed, including the first reports of *Mycobacterium malmoense* adenitis in Canada.

Key Words: Adenitis; *Malmoense*; *Mycobacteria*; Nontuberculous

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that commonly infect immunocompetent children. In contrast with developing countries, where *Mycobacterium tuberculosis* is more common, NTM are the chief cause of subacute and chronic adenitis in North American children, with cervical disease being the most typical presentation (1,2). Although the most frequently isolated species in North America have been *Mycobacterium avium-intracellulare* (MAI), *Mycobacterium scrofulaceum* and *Mycobacterium kansasii*, other NTM species have emerged in recent years (2-4). A low index of suspicion for NTM adenitis frequently results in diagnostic delays, multiple courses of antibiotics and delayed referral for surgical excision. The diagnostic dilemma is compounded by the broad differential diagnosis of an enlarged lymph node.

The present report reviews a decade of experience with NTM adenitis at a pediatric referral centre, including the first two reported Canadian cases of *Mycobacterium malmoense* adenitis, and presents key diagnostic features of this disease along with a suggested algorithm for approaching cervical adenitis. The literature on NTM adenitis is summarized, and the evolving role of new molecular diagnostic techniques is discussed, along with advances in antimicrobial therapy and implications of the emerging mycobacterial species.

Premiers rapports canadiens de l'adénite cervicale causée par le *Mycobacterium malmoense* et analyse décennale de l'adénite mycobactérienne non tuberculeuse

Le présent rapport analyse une décennie d'expérience à l'égard de l'adénite mycobactérienne non tuberculeuse dans un centre spécialisé en pédiatrie et souligne que les patients sont souvent soumis à de multiples antibiothérapies inefficaces et que les retards de diagnostic et d'aiguillage avant de parvenir à un traitement adéquat sont monnaie courante. Les principales caractéristiques cliniques incluent un âge moyen de 3,4 ans à la présentation, un ratio garçons : filles de 1:1,5 et l'apparition graduelle d'une adénopathie cervicale unilatérale indolore. La plupart des patients ne faisaient pas de fièvre (77 %), et la maladie ne réagissait pas aux antistaphylococciques. Le temps moyen avant de poser le bon diagnostic était supérieur à trois mois (15 semaines). Les caractéristiques cliniques de la maladie sont soulignées et présentées selon une démarche diagnostique pratique vis-à-vis de l'enfant atteint d'adénite subaiguë ou chronique. De nouveaux outils diagnostiques moléculaires et les mycobactéries émergentes sont abordés, y compris les premiers rapports d'adénite à *Mycobacterium malmoense* au Canada.

CASE PRESENTATIONS

Patient 1

A previously well two-year-old girl presented to her family physician with several days of painless left-sided submandibular swelling. There was no history of fever, rashes, trauma or recent teething. She had no night sweats, weight loss or tuberculosis contacts.

Cloxacillin therapy was initiated and changed to cephalexin on day 5 when no clinical improvement was noted. Follow-up on day 10 found that the swelling had actually increased. A complete blood count was performed, and all cell counts were found to be normal. Serology was sent for cytomegalovirus, Epstein-Barr virus, *Bartonella henselae* and mumps. By day 20, serology tests had returned negative, yet the swelling remained. Her parents were increasingly anxious.

The patient was referred to pediatric otolaryngology at the IWK Health Centre (Halifax, Nova Scotia) for an excisional biopsy. Preoperatively, a purified protein derivative (PPD) tuberculin skin test was nonreactive and chest radiograph was normal. Computed tomography (CT) scan images of the involved area revealed a large rim-enhancing node with central necrosis and overlying soft tissue swelling (Figure 1).

It was decided to use preoperative clarithromycin pending surgery. Despite this, a fistula to the skin developed with

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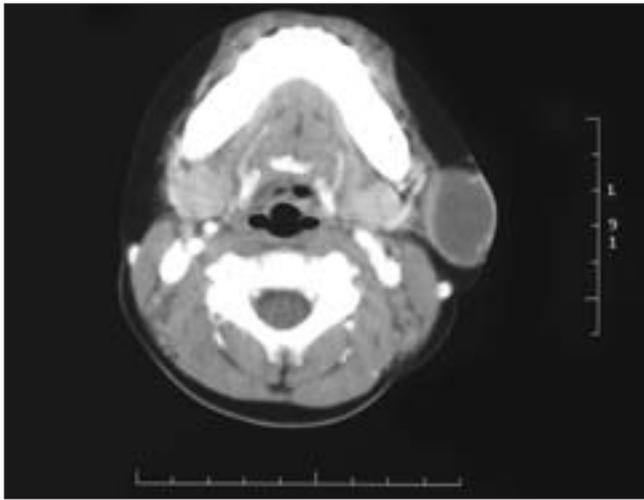


Figure 1) Computed tomography scan of the neck. A large, left-sided rim-enhancing node is present

intermittent drainage. Following excision, histopathology from the lymph node demonstrated necrotizing granulomas consistent with NTM adenitis (Figure 2). Several weeks later, the mycobacterial culture grew *M malmoense* – a species not previously reported to cause extrapulmonary disease in Canada. Cure was achieved with the surgery, and no residual disease was detected on follow-up.

Patient 2

Similar to patient 1, this patient was a healthy two-year-old girl who presented with a painless, submandibular swelling without fever. Early referral to pediatric surgery was done, and surgery arranged with the clinical impression of a branchial cleft cyst. Intraoperatively, necrotic lymph node material was encountered, prompting a revision of the diagnosis to lymph node abscess. An excisional biopsy was performed, and tissue was cultured but not sent for histology. Cephalexin was prescribed postoperatively. Several weeks later, the mycobacterial culture (added as per the laboratory procedure for nodes with negative Gram stains) grew *M malmoense*.

METHODS

Study setting

The study was conducted at the IWK Health Centre, a tertiary care pediatric hospital and the only centre in the province with pediatric otolaryngologists, pediatric surgeons or pediatric infectious diseases staff. The referral base for this centre encompasses the entire province of Nova Scotia and much of the surrounding Maritime provinces.

Study design

A retrospective study of all patients with a diagnosis of mycobacterial adenitis was performed from January 1, 1995, to January 1, 2005. A microbiology database was also searched for any lymph node specimens submitted for mycobacterial culture.

Target population

Patients were included in the study if they had a clinical history and physical examination consistent with mycobacterial adenitis and one of the following inclusion criteria: positive NTM cultures;

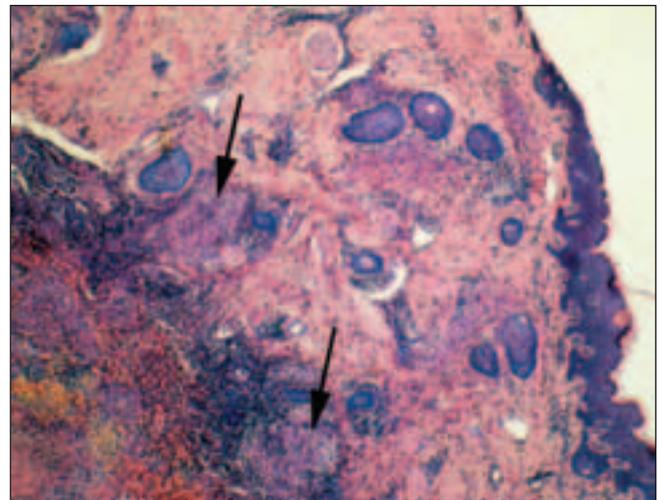


Figure 2) Photomicrograph of node biopsy (original magnification ×60). Note keratinized epithelial margin on the right, granulomas (arrows), and an area of necrosis in the lower-left corner

pathological findings of necrotizing or caseating granulomatous lesions or acid-fast bacteria; or borderline or positive skin test to PPD tuberculin. Ethics approval was obtained from the Izaak Walton Killam Health Centre Ethics Research Board to review charts.

Review of medical records

Medical records were reviewed for all patients identified by the above methods. Demographic and clinical data were recorded on coded data entry forms.

RESULTS

Twenty-five patients with NTM adenitis were identified during the study period (Table 1), all of whom were younger than eight years of age. Based on the last Canadian census, the annual incidence of NTM adenitis in Nova Scotian children under 10 years of age is 2.4 cases/100,000 children (5). The mean patient age was 3.4 years, and 60% were female. All of the patients were immunocompetent. All patients had unilateral cervicofacial lymphadenitis, and multiple nodes were involved in 48% of cases. Onset and progression of swelling was typically described as gradual. Most children (80%) had no history of fever and although some children reported mild tenderness on palpation, most involved nodes were painless (72%). Virtually all children received antistaphylococcal antibiotics before correct diagnosis, with several children exposed to four different antibiotics. Notably, only three of 25 children (12%) were correctly diagnosed within a month of symptom onset. Following diagnosis, seven of 25 children (28%) received antimycobacterial antibiotics in conjunction with surgery. One child had an NTM adenitis adjacent to the facial nerve and was successfully treated with a prolonged course of antimicrobials without surgery.

There were only three recurrences (12%) following surgical resection; two were treated with a combination of antimycobacterial antibiotics and surgery, and one with surgery alone. None recurred after the second round of interventions.

Histopathology demonstrated necrotizing granulomas or acid-fast bacilli consistent with mycobacterial infection in 22 of 24 patients (92%); data were not available for one of the

TABLE 1
Summary of reported cases of pediatric atypical mycobacterial infections

Patient	Year	Age (years)	Sex	Diagnostic delay (weeks)	Fever	Pain	Multiple nodes involved	PPD	Culture result	Granulomas or AFB on histology
1	1996	4.5	F	6	N	N	Y	N/A	NEG	Y
2	1997	6.2	F	4	N	Y	Y	POS	MAI	Y
3	1997	3.5	M	4	N	Y	Y	N/A	MAI	Y
4	1998	2.5	M	10	N	N	N	N/A	NEG	Y
5	1998	1.4	M	12	Y	Y	N	N/A	NEG	Y
6	1998	4.0	F	3	N	N	Y	N/A	MAI	Y
7	1998	1.3	M	8	Y	Y	Y	POS	MAI	Y
8	1999	3.5	M	16	N	N	N	N/A	MAI	Y
9	1999	7.2	F	1	N	N	Y	N/A	NEG	Y
10	1999	4.5	F	20	N	Y	N	N/A	NEG	Y
11	2000	2.4	F	6	N	N	Y	N/A	MAI	N
12	2000	2.6	F	6	N	N	Y	N/A	MM	N/A
13	2000	2.0	F	4	N	N	N	N/A	NEG	Y
14	2000	5.1	F	3	Y	Y	N	POS	NEG	N
15	2001	4.0	M	104	N	N	Y	N/A	NEG	Y
16	2001	3.0	F	24	N	N	Y	N/A	NEG	Y
17	2001	2.1	F	24	N	N	N	POS	NEG	Y
18	2001	4.9	M	N/A	N	N	N	N/A	NEG	Y
20	2001	2.0	F	8	N	N	N	NEG	MM	Y
21	2001	3.3	F	24	N	N	Y	N/A	NEG	Y
22	2002	7.0	M	10	Y	Y	N	NEG	NEG	Y
23	2002	2.0	F	N/A	N	N	Y	N/A	MAI	Y
24	2003	1.2	M	5	Y	N	N	NEG	NEG	Y
25	2003	3.8	M	8	N	N	N	N/A	NEG	Y

AFB Acid-fast bacilli; F Female; M Male; MAI *Mycobacterium avium-intracellulare*; MM *Mycobacterium malmoense*; N No; N/A Not applicable; NEG Negative; POS Positive; PPD Purified protein derivative; Y Yes

patients. In addition, resected nodes were cultured for mycobacteria but yielded positive results in only 40% of cases, including several with nonspecific histological changes. No specimens were tested by nucleic acid amplification techniques.

DISCUSSION

With the decline of *M tuberculosis* in North America and Europe, NTM have emerged as the most frequent cause of subacute/chronic adenitis in children (1,4,6). These low-virulence, acid-fast bacilli are ubiquitous and are found in soil, salt and fresh water, foodstuffs and even air samples (7,8). Cervicofacial adenitis is the most common presentation, followed by inguinal and axillary adenitis (3,9) – a pattern likely explained by entry of these opportunists across respiratory and oral mucosa with subsequent involvement of regional lymph nodes. Otherwise, invasive disease is rare in immunocompetent children.

The nearly exclusive occurrence of NTM adenitis in young children is perhaps a combination of immature immunity and increased exposure of their oral mucosa to environmental organisms due to hygienic habits and pica. Disease incidence varies widely with geographic location. Our calculated rate of 2.4 cases/100,000 children is higher than previously reported North American rates (10).

NTM adenitis continues to be a diagnostic challenge for primary care physicians with limited exposure to the disease. Similar to the findings of Panesar et al (3), we found the typical presentation to be a gradual onset of painless unilateral

cervicofacial adenitis, with constitutional symptoms rarely present. Untreated, the nodes gradually enlarged with skin discoloration preceding fistula formation and external drainage. Lack of response to antistaphylococcal antibiotics is a hallmark. In contrast, acute bacterial adenitis has a more rapid onset and is usually associated with significant pain, dramatic swelling, marked erythema and warmth. Fever is usually present with acute bacterial adenitis and the disease either responds rapidly to antistaphylococcal antibiotics or evolves into a fluctuant mass within several days.

M tuberculosis adenitis, although less common in North America, must be considered in the differential diagnosis, and all patients with suspected NTM adenitis should have a PPD skin test and chest radiograph. In Canada, patients are more likely to have *M tuberculosis* adenitis if they are Aboriginal or foreign-born (10). Other features associated with *M tuberculosis* adenitis are a strongly positive PPD, abnormal chest radiograph, constitutional symptoms, older age and history of a tuberculosis contact (11-14). Posterior cervical adenitis and supraclavicular adenitis have also been associated with increased probability of *M tuberculosis* infection (15).

Other infectious considerations include cat scratch disease, mumps, Epstein-Barr virus infection or cytomegalovirus infection (13,16). History, then, should include cat exposures, vaccination history and recent pharyngitis.

CT scanning is performed preoperatively on the majority of patients today, both as a baseline study and to delineate grossly involved nodes and their proximity to critical neurovascular

structures. This enables surgeons to anticipate potential complications in advance. Inclusion of the mediastinum and lungs should be done on any patients with strongly positive PPD reactions. Follow-up CT is also useful for patients with suspected recurrences or for monitoring patients with disease adjacent to neurovascular structures who are treated with antimicrobials alone.

While a provisional diagnosis may be made on clinical grounds, laboratory-based confirmation has traditionally relied on a combination of histopathology and mycobacterial culture. Histopathology often documents supportive but nonspecific changes, such as granuloma formation, and is valuable in excluding other diseases such as lymphoma. It cannot, however, always differentiate between the various causes of granuloma formation (ie, cat scratch disease versus mycobacterial infection) or, if acid-fast bacteria are seen, distinguish *M tuberculosis* from NTM species. Culture-based diagnosis suffers from poor sensitivity and a slow turn-around time, which hamper the ability to make timely clinical decisions.

Rapid molecular-based techniques for diagnosing NTM infections are increasingly used and have the potential to replace traditional laboratory methods (17). Commercial DNA probes have been available for some time (AccuProbe, Gen-Probe Inc, USA) and offer the ability to speciate mycobacteria grown in solid or broth cultures in as little as 2 h. However, this still creates a time lag until a positive culture is detected, and probes are not available for all pathogenic mycobacteria. To circumvent this, real-time polymerase chain reaction (PCR) is increasingly being used to obtain a specific diagnosis of mycobacterial infection directly from clinical specimens. With mycobacterial adenitis, the test can be applied to tissue obtained preoperatively via needle aspiration or postoperatively using tissue from the excisional biopsy (18-20). This approach has the potential to provide a specific diagnosis in hours, thereby avoiding weeks of waiting on the results of mycobacterial culture. More important, it appears that the sensitivity of molecular tests has surpassed the sensitivity of culture. A recent report (20) of real-time PCR used for the diagnosis of mycobacterial adenitis found that real-time PCR detected mycobacteria in 48 of 67 patients (71.6%), while auramine staining and culture detected mycobacteria in 31 of 67 (46.3%) and 28 of 67 (41.8%) patients, respectively. Because multiple mycobacterial species may cause adenitis, PCR-based approaches typically use either a multiplex PCR to look for the most significant species (ie, MAI or *M tuberculosis*) or amplify a shared mycobacterial DNA segment (such as the gene coding for the 16S ribosomal RNA), then sequence the amplicon to speciate the organism. With the automation of sequencing, the latter approach is becoming feasible for many laboratories. While the first standardized real-time PCR commercial kits for *M tuberculosis* are becoming available, molecular detection of NTM remains largely through 'home-brewed' in-house assays, making it a challenge to standardize results or compare tests from different centres.

Novel, less invasive applications of PCR in the diagnosis of mycobacterial adenitis have included the detection of mycobacterial DNA from peripheral blood or gastric aspirates (21,22). Although only pilot studies on these noninvasive approaches have been performed, the preliminary data are interesting.

While surgical management has long been the gold standard for therapeutic intervention, a number of techniques

have been touted. Panesar et al (3) reviewed published success rates with various surgical methods (ie, curettage versus complete resection) and concluded that complete surgical excision remains the procedure of choice. Early resection has been associated with improved cosmetic outcome (23). The high recurrence rates associated with incision and drainage procedures should preclude their use in most situations. The 88% success rate of surgery in our centre is consistent with previously published experience.

The isolation of *M malmoense* from two patients represents the first reports of extrapulmonary disease due to this organism in Canada. Identification was confirmed via high performance liquid chromatography at Laboratoire de santé publique du Québec (Quebec) using the Sherlock Mycobacteria Identification System (MIDI Inc, USA).

M malmoense was first isolated in 1977 from four adults with pulmonary disease, and is named after the city of Malmo, Sweden, where these patients lived (24). Subsequently, the organism emerged in northern Europe and the United Kingdom as a cause of MAI-like pulmonary disease in adults and as a rare cause of pediatric adenitis (25). In 1980, *M malmoense* appeared in the United States (26), and the sole Canadian report to date was in an adult with pulmonary disease (27). Over the past decade, *M malmoense* has been described more frequently in the United States, where it is now considered to be an emerging NTM species (28).

Nonpigmented in all light conditions, *M malmoense* is classified as a nonphotochromogen belonging to Runyon Group III. Among the most fastidious NTM, some strains require up to 12 weeks of incubation, well beyond the duration many laboratories hold cultures.

The introduction of new antibiotics and standardization of NTM susceptibility testing has strengthened the role of antimicrobials as an adjunct to surgery for cases where complete surgical excision cannot be assured (ie, involvement of neurovascular bundles). One recent paper (29) even challenges the concept that most mycobacterial adenitis cases should receive surgery as a first-line intervention. Contrary to the current dogma on this disease, the authors demonstrated that 30 of 45 patients (67%) were cured with antibiotics alone. Clarithromycin was used alone in most cases and, at the physician's discretion, sometimes combined with other antimicrobials including rifampin, ethambutol and/or ciprofloxacin. This mirrors the empirical antibiotic choices made in most centres today. In areas where *Mycobacterium avium* complex are the most common NTM species, clarithromycin plus rifabutin or ciprofloxacin has been recommended by some authors (30,31). When a specific organism is identified, therapy can be tailored. The statement "Diagnosis and treatment of nontuberculous mycobacteria", made by the American Thoracic Society, provides therapeutic guidelines for various NTM species (32). Duration of therapy is individualized, based on clinical and radiological response, but is generally a minimum of three months. Courses of six to 12 months may be necessary in selected cases. Among newly available antimicrobials, linezolid (from the oxazolidinone class) has recently been shown to have broad antimycobacterial activity against most NTM species, including *M malmoense* (33). Future experience may clarify its role in the management of NTM adenitis.

NTM adenitis is an increasingly common pediatric infection. Although *Mycobacterium avium* complex remains the most common causative agent, diverse NTM species are

emerging. Early and complete surgical excision remains the treatment of choice. Definitive diagnosis may be accelerated by new molecular diagnostic techniques. Antibiotic therapy alone is an option for unresectable nodes and perhaps other selected patients, but this requires months of therapy and is optimally guided by species identification and selected antimicrobial susceptibility testing.

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