ABSTRACT. Pulmonary disease caused by nontuberculous mycobacteria (NTM) is a relatively rare occurrence in immunocompetent children. Two cases of endobronchial NTM infection in immunocompetent children are described. In addition, 41 other children with NTM pulmonary disease reported in the English literature between 1930 and 2003 are reviewed. Clinical manifestations are either purely respiratory or respiratory with more widespread systemic symptoms. Compared with children with only respiratory complaints, children with constitutional symptoms from NTM pulmonary disease 1) had symptoms for a shorter period before presentation (10 vs 28 days), 2) had more radiographic evidence of pulmonary disease, and 3) were treated longer with antimycobacterial agents (11.5 months vs 6 months). The most common causative organism was Mycobacterium avium complex. Pediatricians should be increasingly aware of NTM in the differential diagnosis of persistent pulmonary disease in previously healthy children. *Pediatrics* 2003;112:e434-e439. URL: http://www.pediatrics.org/cgi/content/full/112/5/e434; *atypical mycobacteria, Mycobacterium, lung disease, respiratory tract infections.*

**ABBREVIATIONS.** NTM, nontuberculous mycobacteria; CT, computed tomography; INH, isoniazid; PZA, pyrazinamide; MAC, *Mycobacterium avium* complex.

Nontuberculous mycobacteria (NTM), ubiquitous organisms in the environment, historically have not caused invasive disease in immunocompetent hosts. However, increasing numbers of case reports document the spectrum of disease caused by these bacteria in otherwise healthy individuals in the past 2 decades. By far, the most common expression of infection with NTM in immunocompetent children is lymphadenitis, whereas pulmonary disease has been a relatively rare occurrence.¹ Two cases of endobronchial NTM infection in immunocompetent children are reported. In addition, all pediatric cases of NTM pulmonary disease reported in the English literature between 1930 and 2003 are reviewed.

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Received for publication May 2, 2003; accepted Jun 25, 2003.
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**CASE REPORTS**

**Case 1**

A 2-year-old white girl with a history of reactive airway disease was hospitalized in August 1998 after 2 weeks of a mild nonproductive cough, wheezing, and fatigue. There was no history of recent fever and she was afebrile on admission. Mild bilateral wheezing was found on physical examination. Her chest radiograph showed an opacity in the upper right perihilar region (Fig 1), which was further defined on computed tomography (CT) as a 3-cm suprahilar mass compressing the right mainstem bronchus. Bronchoscopy revealed a fleshy endobronchial mass just distal to the carina that occluded 80% of the right mainstem bronchus. In addition to routine bacterial cultures, bronchial wash was sent for mycobacterial culture and acid-fast stain. Morning gastric aspirates, collected on 3 consecutive days, were negative. Subsequent biopsy showed necrotizing granulomata and acid-fast bacilli.

A 5-tuberculin unit skin test was placed and measured 16 mm. During source case investigation, the mother was found to have a tuberculosis skin test measuring 10 mm, and the father and the brother had tuberculin skin tests measuring 12 mm. Chest radiographs of immediate family members were normal. The patient was started on isoniazid (INH), rifampin, and pyrazinamide (PZA) after biopsy. Prednisone was used to reduce the endobronchial inflammation.

Six weeks later, *Mycobacterium avium* complex (MAC) was cultured from the bronchoalveolar lavage, 1 of 3 gastric aspirates, and the bronchial mass. Susceptibility tests were still pending. INH and rifampin were continued for 6 months to complete *M tuberculosis* treatment and because the patient clinically improved during her empiric therapy. Azithromycin was added as empiric therapy for MAC. PZA was discontinued after the initial 8 weeks. Subsequent susceptibility testing performed by the National Jewish Center for Immunology and Respiratory Medicine interpreted the isolate to be sensitive to clarithromycin but resistant to INH, PZA, and rifampin. All antibiotics were discontinued after 6 months. White blood cell counts and differentials were always normal. Testing for human immunodeficiency virus was negative.

**Fig 1.** Chest radiograph of patient 1 shows opacity of upper-right perihilar region.
Three months after the initial evaluation, the chest radiograph was much improved. The patient continues to do well clinically 5 years later without recurrent MAC or other systemic infections. Explanations for the positive tuberculin skin tests on the other family members include either latent *M. tuberculosis* or a similar exposure to MAC.

**Case 2**

A previously well 13-month-old white boy presented to his primary doctor in June 2001 with a mild cough for 6 weeks. The patient was noted to have asymmetrical breath sounds. He was admitted for evaluation of a possible foreign-body aspiration. His examination was notable for diffuse rhonchi and wheezing on auscultation. He was afebrile and in no acute respiratory distress unless supine, at which time he was mildly stridulous. A chest radiograph showed hyperinflation of the left lung with a mediastinal shift to the right. There was an opacity noted in the left suprahilar region. A chest CT showed a diffusely lucent left lung and adenopathy adjacent to the left mainstem bronchus, with a mild narrowing of the distal left bronchus and the presence of foreign material within that bronchus (Fig 2).

The patient was placed on intravenous ampicillin/sulbactam and steroids. He also underwent bronchoscopy on several occasions because the attending surgeon wished to document clearance of the foreign material. The first procedure revealed granulation tissue in the left mainstem bronchus. Close surgical observation eventually revealed the persistence of a granulomatous, “cheesy,” and friable lesion seen at the left mainstem bronchus. There was extraluminal compression of the bronchus.

Histology showed granulation tissue with necrosis; acid-fast bacilli were present. A 5-tuberculin unit skin test, performed while the child was on steroids, was negative. Collection of only 1 morning gastric aspirate was completed. The patient was started on INH, rifampin, and PZA and continued on steroids. Extensive tuberculin testing of household and close contacts was negative.

The mycobacterial culture from 1 bronchoscopy was positive for MAC. After the isolate was identified, the triple antituberculosis medications were discontinued. Azithromycin and ciprofloxacin were initiated empirically until susceptibilities were available. Three months after initial presentation, a follow-up chest radiograph was improved. Surveillance bronchoscopies conducted every 2 to 3 months has shown the lesion to be shrinking in size. The latest CT (after 8 months of therapy) showed persistent hyperlucent changes in the left lung, a 5-mm calcified granuloma in the left lower lobe, and the continued presence of material in the left bronchus. The hilar adenopathy has since resolved. A repeat pathologic specimen obtained 10 months after diagnosis still exhibited acid-fast organisms. His most recent bronchoscopy at 21 months postdiagnosis revealed complete resolution.

The organism is intermediate in susceptibility to amikacin, resistant to ciprofloxacin and rifampin, and sensitive to clofazimine; the last drug was not started because of potential toxicity. Susceptibility to PZA was not reported. He received a total duration of 10 months of therapy. The patient has remained clinically well without other systemic infections.

**REVIEW OF THE LITERATURE**

The Medline database was searched for cases of NTM lung disease in children. The words “pediatric,” “atypical,” “nontuberculous,” “mycobacteria,” “mycobacterium,” “lung,” “endobronchial,” and “pulmonary” were used. The references of retrieved articles were reviewed for additional reports. Articles reported in the English language were studied. Inclusion criteria were pediatric age (<18 years), previously healthy, and pulmonary disease as defined by chest radiograph and/or direct visualization. Associated cervical adenopathy was not an exclusion criterion; however, any concern with the child’s immune status in the case report was an automatic exclusion from this review. NTM was defined as the sole causative agent by culture or skin test reactivity to NTM antigens. Case reports with alternative causative possibilities, infectious or other, were not included. A comment on clinical presentation was required in the case report.

Forty-three cases of intrathoracic disease in previously well children have been recorded from 1930 to 2003, including the 2 current reported cases (Table 1). Three reports of NTM intrathoracic disease appeared in the English literature for the 30-year span of 1930–1960. Fifteen cases were described in the period 1961–1990, a 5-fold increase. In the period 1991–2003, 25 cases (including these 2) have been reported.
Clinical Presentation

All children presented with cough and/or wheezing. They seemed to fall evenly into 2 categories: those who presented with constitutional and respiratory symptoms (group 1) and the others with only respiratory complaints (group 2; Table 2).

Group 1 (Systemic Presentation)

Twenty-six (60%) of 43 patients had accompanying constitutional complaints, including our first case. These children came to medical attention after a median of 10 days of illness (range: 1–196 days). After respiratory complaints, the most common systemic symptom was fever (23 patients). The median duration of fever before presentation was 12 days (range: 1–196 days). Nine patients presented with accompanying complaints of anorexia/weight loss. Fatigue and night sweats were found in 3 children (cases 1, 6, and 7) and in 2 children (cases 26 and 35), respectively.

Group 2 (Only Respiratory Complaints)

Seventeen patients (including our second case) had no constitutional symptoms. The complaints were cough, wheezing, and/or respiratory distress. The median time to diagnosis was 28 days (range: 3–84 days). In 4 cases (cases 2, 8, 10, and 28), a diagnosis of foreign-body aspiration was suspected initially.

Age, Sex, and Ethnicity

The median age was the same for both clinical presentations (24 months). The male to female ratios were essentially equal. In reports including ethnic origin (n = 14), 10 children were white.

Isolated NTM Species

The majority of pulmonary isolates were MAC in both clinical groups.

Tuberculin Skin Test Measurements

The average tuberculin skin test measurement was the same for both groups (7 mm; data not shown).

Invasive Procedures

Many patients underwent >1 diagnostic procedure. The procedures most frequently noted to yield...
positive cultures were gastric washings ($n = 12$) and endobronchial biopsies ($n = 10$). Other positive cultures were derived from lymph node biopsy ($n = 8$), sputum ($n = 4$), bronchoalveolar lavage ($n = 3$), pleural effusion ($n = 2$), or lung tissue biopsy ($n = 2$). A portion of cases were presumptively diagnosed by reactivity to nontuberculous mycobacterial skin testing ($n = 5$).

**Chest Radiographs**

One third of chest radiographs from each group had evidence of asymmetric air trapping. Group 1 (systemic complaints) had more infiltrates (77%) compared with the respiratory group (47%). Group 2 had a similar percentage of unilateral disease (65%) as the purely respiratory group (52%). Both groups had a low rate of pleural effusion (0%–7%); hilar adenopathy was observed in nearly half (41%–46%). No child had any radiographic description of cavitary or bullous lung lesions.

**Therapy and Clinical Outcome**

Patients with systemic complaints were treated for almost twice as long (median: 11.5 months; range: 13 days to 17 months) as the group with only respiratory symptoms (median: 6 months; range: 2–13 months). Therapeutic surgical intervention (debulking of the endobronchial mass, lobectomy) was reported in 12 cases (excluding 2 cases of cervical node surgery). The intervention was reported in both group 1 (7 cases) and group 2 (5 cases).

Only 2 surgical interventions were reported before 1981. Specific comments on sequelae and length of follow-up were lacking in 14 case reports. No serious sequelae were noted in two thirds of the patients in each clinical group despite differences in specific antituberculous drugs and duration of anti-NM therapy. Persistently abnormal radiographic findings were observed in 6 patients, with follow-up ranging from 9 months to 3 years.

Only 3 patients were reported to experience relapse of their pulmonary disease. Case 43 had a worsening radiograph 1 year after initial presentation. Cases 12 and 16 had clinical and radiographic evidence of relapse. Case 12 experienced bronchial compression 4 weeks after lobectomy and required local resection. Case 16 had right lower lobe changes that occurred 1 week before completing his 12-month therapy.

**DISCUSSION**

NTM are ubiquitous acid-fast organisms found throughout nature. Historically classified by Runyon and Runyon in the 1950s according to the 3 characteristics of rate of growth, colony pigmentation, and colonial morphology, they are now simply grouped by rapidity of growth. Speciation occurs through a variety of biochemical, morphologic, and physiologic tests. Fewer than half of the known 50 species of *Mycobacteria* cause human disease.

NTM species have a predilection to be found in different geographic environments. In the United States, MAC disease has historically been localized to coastal borders and states that border Canada. MAC is also the dominant species causing disease in other countries such as Australia. *M. kansasii* is most commonly seen in the midwestern United States. Person-to-person transmission of NTM has not been reported.

The route of entry of NTM into the body is unknown. In cervical adenitis seen in children, ingestion of contaminated soil or water is speculated to be the source of infection, with the oropharynx as the portal of entry. In cutaneous disease, infection is thought to be from direct contact of a nonintact integument with organisms. It is interesting to speculate that pulmonary infection is acquired through inhalation of aerosolized organisms, particularly through water droplets. A number of case reports attribute pulmonary disease to hot-tub use, when organisms may be readily aerosolized.

Historically, NTM have been a cause of serious disease in immunocompromised hosts. In contrast, healthy pediatric hosts have mild infection, such as superficial adenopathy or cutaneous lesions. In-
INTRATHORACIC DISEASE FROM NONTUBERCULOUS MYCOBACTERIA

Rise in Reported NTM Pulmonary Disease in Healthy Children

Several clinicians have remarked on the increasing number of NTM cases in the past 2 decades. Although an actual incidence of cases of NTM is not available because it is not included in mandatory state reporting, it is estimated to be 1 to 1.8 cases/100,000 population in the United States. Wolinsky summarized the epidemiologic trends in the United States: 1) NTM disease is increasing in actual numbers and in proportion of disease, and 2) MAC is the dominant NTM species.

Our case series is the first to document an increasing trend of NTM disease reported in the literature during the past 70 years. This may be a result of improved methods of culturing and identifying organisms, more sophisticated diagnostic techniques (CT, invasive diagnostic procedures), and increased interest. However, population data would be necessary to verify this increasing trend.

Clinical Presentations

Two populations in which disease caused by NTM has been recognized previously are adults with intrapulmonary disease and children with cervical adenitis. In this report, we described a third population, in which children with intrathoracic NTM disease can present with either systemic or purely respiratory symptoms. This differentiation of clinical presentations of NTM pulmonary disease was observed by Huang et al in the adult population. They noted that all of their adult patients with NTM pulmonary disease (a retrospective review of 31 outpatient subjects) had a chronic cough. Half (48%) also had constitutional complaints, similar to the reports in the pediatric literature. In a brief survey of the literature on pediatric cervical adenitis secondary to NTM, no delineation of clinical presentations was found. The vast majority of children with NTM cervical adenitis were otherwise healthy-appearing.

Age, Sex, and Ethnicity

Children with pulmonary infection caused by NTM are similar to those with cervical adenitis with regard to age, sex, and ethnicity. The majority of patients with disease (or infection) by NTM are white. This may reflect better case-finding procedures for whites than for other ethnicities, but this trend remains consistent over time. When NTM causes either cervical adenitis or intrathoracic infection, the target population is white children in the toddler age group.

Chest Radiographs

In general, children with pulmonary disease caused by NTM have a radiographic picture similar to that commonly observed with M tuberculosis, with mediastinal and hilar lymph node involvement. Group 1 (systemic complaints) had more radiographic abnormalities, perhaps reflecting observer bias on more sick children. In our review, the children with advanced disease (signaled by generalized complaints) had increased infiltrates compared with children with only respiratory complaints.

Therapy and Clinical Outcome

Over time, better antibiotic therapy and improved diagnostic techniques have been developed. Although the collected data are not presented in detail, in the more recent years of this literature review, there has been a trend toward increasing the duration of antibiotic therapy in patients with pulmonary infection caused by NTM. Otherwise healthy patients with only respiratory symptoms were treated for 8.2 months, whereas children with more severe presentations were treated for 9.6 months. The 1997 recommendation of the American Thoracic Society that pulmonary disease in adults be treated for 10 to 12 months. No standard therapeutic regimen exists for children.

Eleven (25%) of 43 cases underwent at least 1 surgical procedure, particularly in the last decade. This may reflect more comfort in performing invasive surgical techniques in children, increasing incidence of disease, or increasing severity of NTM pulmonary disease in children. The lack of denominator data on all procedures done precludes definitive recommendations on the best test to diagnose NTM in pediatric lung disease.

A discussion of the therapy of infections caused by NTM is complicated. Many strains of mycobacteria that cause infection in children, either cervical adenitis or pulmonary disease, are resistant to INH, rifampin, and PZA. However, these agents are likely to be initial therapy when pulmonary infection caused by M tuberculosis is suspected. Drugs that might be added for suspected NTM disease include azithromycin, clarithromycin, and ciprofloxacin. By the time susceptibility results are available, the patient may have been treated for approximately 4 months with a collection of antibiotics to which the organism is not susceptible, which was the case for our 2 patients.

The experience with pediatric cervical adenitis from NTM may be applicable to intrathoracic disease in children. The natural history of cervical adenitis caused by NTM is resolution over 12 to 18 months. It is unclear whether medical therapy with antituberculous drugs hastens recovery. Surgical excision results in more rapid clinical cure; however, the ultimate cosmetic and medical results of surgical intervention and observation are similar. The need for or effectiveness of antimicrobial therapy for pulmonary NTM has not been established in immunocompetent children.

Our 2 case reports originated in western Pennsylvania, an area without a documented case of primary pulmonary tuberculosis in a pediatric patient in 6 years. Regional differences in incidence of M tuberculosis will have an impact on the differential diagnosis that a clinician develops. In areas where M tuberculosis is less prevalent, NTM should be suspected in immunocompetent children with persistent pulmonary disease.
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