Skin Indurations in Response to Tuberculin Testing in Patients with Nontuberculous Mycobacterial Lymphadenitis

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Mantoux results were examined for 29 children with culture-proven nontuberculous mycobacterial lymphadenitis, and 4 species were isolated: Mycobacterium avium-intracellulare complex (from 14 patients [48%]), Mycobacterium haemophilum (from 12 [41%]), Mycobacterium simiae (from 2 [7%]), and Mycobacterium scrofulaceum (from 1 [3%]); the median indurations for each species were 15.5 mm, 14.5 mm, 20 mm, and 23 mm, respectively, and in 17 cases (59%), they were ≥15 mm. In regions with a low incidence of tuberculosis, lymphadenitis thought to be due to nontuberculous mycobacteria should be managed as such, regardless of Mantoux results, thereby avoiding antituberculosis treatment.

Nontuberculous mycobacteria are ubiquitous organisms that can cause various clinical syndromes. The most common manifestation in children is cervical lymphadenitis; bone, joint, skin, soft-tissue, pulmonary, catheter-related, and disseminated infections are much less common [1]. A definitive diagnosis requires isolation of nontuberculous mycobacteria from a sterile site. However, presumptive diagnoses are often made on the combined basis of clinical findings (e.g., cervical lymphadenitis), epidemiological features (e.g., population with low prevalence of tuberculosis), and positive results of tuberculin skin testing.

Nontuberculous mycobacterial infections are usually associated with an induration of 3–15 mm on the standard intradermal tuberculin test (5 TU) [1], because purified protein derivatives (PPD) from Mycobacterium tuberculosis share common antigens with nontuberculous mycobacteria. Although the size of the reaction overlaps in M. tuberculosis infection and in infections with nontuberculous mycobacteria, an induration of ≥15 mm is considered to be more indicative of M. tuberculosis infection. A reaction of <15 mm (usually 5–9 mm) in a patient aged 1–4 years with cervical lymphadenitis, normal findings on a chest radiograph, other family members nonreactive to M. tuberculosis PPD, and no exposure to an adult with tuberculosis is more likely to indicate nontuberculous than tuberculosis mycobacterial infection [2].

During the past few years, many of our patients with culture-proven nontuberculous mycobacterial lymphadenitis, who had neither history of exposure to tuberculosis nor clinical or radiological evidence of tuberculosis, nevertheless had reactions to M. tuberculosis PPD of ≥15 mm. In this retrospective study, we examined the sizes of intradermal indurative reactions to the tuberculin test among children with culture-proven nontuberculous mycobacterial lymphadenitis.

Methods. The medical records of Schneider Children’s Medical Center of Israel (Tel Aviv) were reviewed for all patients who were suspected of having infections with nontuberculous mycobacteria or tuberculosis and who attended the day care unit in 1995–2000, and the registry of the hospital’s microbiology laboratory was reviewed for all diagnoses of culture-proven nontuberculous mycobacterial infection and tuberculosis within the same period. All culture samples were obtained by needle aspiration and isolated as described elsewhere [3]. M. tuberculosis PPD (5 TU; Pasteur Mérieux Connaught) was used for skin testing. For all patients, the size of the maximum indurative reaction was measured using the ball-pen method by the same infectious disease specialist (J.A.) 48–72 h after placement. The following data were also recorded: site of infection, mycobacterial species isolated, relevant physical findings, findings on a chest radiograph, history of exposure to tuberculosis, tuberculin test results for family members, BCG vaccination status, and demographic characteristics. The statistical tests used were Pearson’s correlation and analysis of variance.

Results. Sixty-five generally healthy patients aged 1–21 years (median age, 3 years) were evaluated for suspected nontuberculous mycobacterial lymphadenitis. Culture-proven nontuberculous mycobacterial infections were identified in 29 patients (15 male and 14 female patients; age range, 8 months to 18 years; median age, 2.5 years). Eight patients had presumed tuberculosis (3 male and 5 female patients; age range, 1.5–21 years; median age, 14 years); tuberculosis was culture-proven...
in 3 patients (1 male and 2 female patients; age range, 8.5–21 years; median age, 19 years). None of the patients had been vaccinated with BCG.

The cervical lymph nodes were the site of infection for all patients with nontuberculous mycobacteria. Four species were isolated: Mycobacterium avium-intracellularare complex (from 14 patients [48%]), Mycobacterium haemophilum (from 12 [41%]), Mycobacterium simiae (from 2 [7%]), and Mycobacterium scrofulaceum (from 1 [3%]). The median size of reaction to M. tuberculosis PPD for all species was 16 mm (range, no reaction to 33 mm); the median reactions by species were 15.5 mm (range, 7–33 mm), 14.5 mm (range, no reaction to 30 mm), 20 mm (both patients) and 23 mm, respectively (figure 1). Four patients (14%) had no indurations; 7 (24%) had indurations of <10 mm, 12 (41%) had indurations of <15 mm, and 17 (59%) had indurations of ≥15 mm. All patients had normal findings on chest radiographs. No significant statistical correlations were found between induration size and either nontuberculous mycobacterial species or patient age. Two of the patients with pulmonary tuberculosis had a reaction to M. tuberculosis PPD of 30 mm, and 1 had a reaction of 20 mm.

Discussion. This study shows that, in ~50% of immunocompetent children with nontuberculous mycobacterial cervical lymphadenitis, the indurative reaction to M. tuberculosis PPD measures ≥15 mm by the ball-pen method, and in ~25%, it measures <10 mm. Although large indurations have been found among adults infected with various nontuberculous mycobacterial species [4], the incidence of large indurations found here is greater than that reported elsewhere in series of children with cervical lymphadenitis. Wolinsky [5] reviewed results of 105 American children with presumed nontuberculous mycobacterial lymphadenitis (83 culture-proven cases), of whom 91 underwent a PPD skin test; only 7 children (8%) showed indurations of ≥15 mm, whereas 57 (63%) had indurations of <10 mm. In another study from Greece, among 43 of 47 pediatric inpatients with presumed nontuberculous mycobacterial lymphadenitis (40 culture-proven cases) who underwent a tuberculin test, the median induration was 7 mm (range, 0–15 mm), and most patients (70%) had indurations of <10 mm [6].

Differences between our results and those from different parts of the world [5, 6] may indicate the existence of different nontuberculous mycobacterial species and subspecies. This diversity may result from regional environmental factors that affect mycobacterial cell wall structure and, consequently, immunogenicity.

In fact, in contrast to previous reports among children with nontuberculous mycobacterial lymphadenitis [5–7], we had a high isolation rate of M. haemophilum. This might be the result of a high prevalence of this species in our geographic area, but it may also be attributable to our laboratory routine of use of broth with an iron supplement incubated at 30°C for processing aspirated specimens [3]. Correa and Starke [8] claimed that the size of reactions to M. tuberculosis PPD in infections caused by M. avium-intracellularare complex is usually 0–10 mm and rarely exceeds 18 mm, whereas infections caused by other species, especially Mycobacterium marinum and Mycobacterium fortuitum, are frequently associated with reactions of 10–20 mm. Because of scant data, it is impossible to estimate the range of indurative responses to M. tuberculosis PPD in children infected with M. haemophilum in other parts of the world. Nevertheless, our series shows that this species can occasionally be very immunogenic.

Genetic factors can interfere with the response to M. tuberculosis PPD. Differences in the distribution of HLA types may be associated with genetic control of the response to mycobacterial skin tests as well as the individual variability in response to the “common” and species-specific components of mycobacterial antigens [9, 10]. Hence, possible genetic variations among populations may also explain the differences in induration size between our study and earlier ones [5, 6].

Other possible contributors to large M. tuberculosis PPD indurations are M. tuberculosis infection, BCG vaccination, and measurement technique in the evaluation of the skin test. M. tuberculosis infection is unlikely in our patients, because they were all clinically healthy, had no history of exposure to tuberculosis, and recovered completely without antituberculosis therapy. BCG is irrelevant, because none had been vaccinated.
Differences in technique may be a factor, because an average difference of >3 mm has been reported between the ball-pen method and palpation of the induration edges [11]; the ball-pen method is a little more sensitive than is palpation [12].

Starke and Correa [13] recommended that a child with lymphadenopathy and a tuberculin skin test reaction of ≥15 mm should receive antituberculosis treatment even if there is neither an epidemiological history of exposure to tuberculosis nor high rates of tuberculosis in his or her area. Our results point toward a modification of this approach, with consideration of both the experience with Mantoux test responses in nontuberculous mycobacterial infections and the incidence of tuberculosis in a specific region. In areas with high rates of large indurations that result from nontuberculous mycobacterial species and a low incidence of tuberculosis, suspected nontuberculous mycobacteria–induced lymphadenitis in immunocompetent children (1–5 years of age) in the presence of a negative result of mycobacterial culture of aspirate, normal findings on chest radiographs, and no history of exposure to tuberculosis should be managed as a nontuberculous infection, and antituberculosis treatment avoided.

References