The Tuberculin Skin Test: A Useful Screen for Nontuberculous Mycobacterial Lymphadenitis in Regions with a Low Prevalence of Tuberculosis?

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(See the article by Lindeboom et al. on pages 1547–51)

Chronic cervical lymphadenopathy (CCL) presents a familiar diagnostic challenge to pediatricians and adult physicians [1]. Its importance lies not only in the local symptoms and disfigurement that may result; it is often a sign of multifocal disease requiring systemic management. Infectious agents—chief among them the mycobacteria—account for most cases of CCL worldwide. Historically, tuberculous lymphadenitis due to Mycobacterium tuberculosis and Mycobacterium bovis was predominant, typically arising during youth as a metastatic manifestation of uncontrolled primary infection acquired by the respiratory or oral route. After 1950, as tuberculosis (TB) waned and M. bovis disease virtually disappeared from “developed” countries, nontuberculous mycobacteria (NTM) emerged as major agents of CCL, mainly in young children [2–5].

The ascendance of NTM in the differential diagnosis of CCL reflects several epidemiologic factors besides the decrease in rates of TB. In developed countries, the low rates of M. tuberculosis infection and, in some, the cessation of vaccination with bacille Calmette-Guérin have left children more susceptible to symptomatic NTM infection because of a lack of collateral immunity [5, 6]. The number of persons living with chronic immunosuppressive conditions has increased. Changing environmental conditions may also play a role. For example, the decrease in Mycobacterium scrofulaceum and the concurrent increase of M. avium complex (MAC) as a cause of CCL has been attributed to the chlorination of potable water supplies [7]. New species of potentially pathogenic NTM have been recognized at an accelerating rate, as exemplified by Mycobacterium haemophilum as an important agent of CCL in children [8]. Contemporary mycobacteriology offers more-sensitive culture techniques (the routine use of a broth medium and selective solid media) supplemented by new molecular diagnostics, such as PCR [9].

Against a backdrop of growing interest in NTM, the Dutch CHirurgie versus MEDicatie (CHIMED) study on chronic (>3 weeks in duration) cervicofacial lymphadenitis in children [8, 10] is noteworthy for several reasons. In a large prospective survey of this syndrome, the investigators reached an etiologic diagnosis in every case (often by PCR) and performed skin tests using 3 NTM sensitins in 180 of the 210 children who were referred to the study. In the latest CHIMED report, Lindeboom et al. [10] compare these sensitins with a standard tuberculin. Among 112 children whose lymphadenitis was attributed to an NTM, MAC was, as usual, the most common pathogen (74%), followed by M. haemophilum (19%). The M. avium skin test proved to be the most sensitive (94%) for NTM collectively, but the tuberculin skin test (TST) also gave positive results in 70% of those tested, at an optimal cutoff point of ≥5 mm (receiver operating characteristic analysis). Among 62 children with a non-NTM diagnosis, false-positive results were few (≤5%) for all 4 skin tests.

Prior studies that assessed dual or multiple skin tests as a diagnostic tool usually sought a dominant sensitin, on the basis of induration size, to distinguish NTM from M. tuberculosis infection [9, 11, 12]. Instead, given the nonavailability of NTM sensitins to most clinicians, Lindeboom et al. [10] suggest using the TST as a surrogate test to identify children whose CCL is likely NTM induced. This novel approach depends on several provisos: the patient must be at low risk of M. tuberculosis infection and must not be bacille
Calmette-Guérin-vaccinated or immunodeficient. These conditions may apply for otherwise healthy children in selected geographic areas, but the strategy would be invalid in most of the world: most nations practice bacille Calmette-Guérin vaccination, and most humans reside in regions with prohibitively high TB rates. Even in the United States, Canada, and Western Europe there are sizable subpopulations, mainly urban, in whom the prevalence of *M. tuberculosis* infection is $\geq 10\%$. Ongoing immigration from high-risk countries ensures that TB lymphadenitis will remain a diagnostic concern, even in wealthy countries with low TB rates among their native-born population, for the foreseeable future.

Given a positive TST in the appropriate clinical setting, the authors suggest proceeding straight to surgical excision of the diseased lymph node(s). This strategy is effective in that it provides optimal material for culture and histopathology and is usually curative in localized NTM disease [2, 5, 9, 13]. However, it begs the question of chemotherapy for mycobacterial lymphadenitis. Surgery remains the best-established treatment for NTM lymphadenitis [3, 9, 13, 14]. It bypasses the problems of nonadherence to long-term chemotherapy, drug intolerance and toxicity, and difficulties in administering drugs to young children. However, surgery is not always mandatory or even preferred [3, 4, 13, 15]. If TB is diagnosed or cannot be excluded, the extirpation of diseased nodes would not obviate chemotherapy, given the multifocal and persistent nature of *M. tuberculosis* infection. Drugs may contribute to ultimate cure in some NTM infections, particularly in immunodeficient hosts, by controlling foci that are unrecognized or are not readily or safely resectable [14]. Needle aspiration, a lesser invasive procedure, is usually an appropriate first step, provided the patient is stable and can afford to wait several weeks for culture results (depending on the setting, empiric treatment for TB may be appropriate during the interim). Aspiration is preferred when suppuration is apparent (lymph node pus is usually culture positive, and aspiration may relieve discomfort and forestall sinus formation) and when TB is suspected (surgery is unnecessary when culture yields *M. tuberculosis*). In nearly all NTM-induced CCLs, the causal species is potentially drug responsive. The utility of macrolide-based chemotherapy—as an alternative or an adjunct to surgery—has not been adequately studied [4, 14]. The CHIMED trial should clarify its role vis-à-vis surgery, particularly for CCL due to MAC.

What are the potential pitfalls of basing a presumptive NTM diagnosis on a positive TST? Biopsy culture is negative in $\sim 20\%$--$50\%$ of cases of NTM and TB lymphadenitis [3, 5, 9, 11, 14, 16], and PCR is usually unavailable in routine practice. Thus, one may anticipate the occasional misdiagnosis of TB as NTM infection and some instances of unnecessary surgery. The possibility of anergy, either generalized or mycobacterium-specific, remains a background concern [4, 9]. There may be management errors, given the gamut of clinicians who encounter such cases—pediatricians, internists, family practitioners, and surgeons—and their need to be well-informed about mycobacterial disease and the complexities of TST interpretation. One may also question the actual “usefulness” of the proposed TST screening [10] (i.e., how often the result would modify physicians’ diagnostic and therapeutic maneuvers). Some may feel uncomfortable in presuming NTM infection given a child with undiagnosed lymphadenitis and a TST result of 5--14 mm (a larger induration should heighten concern about TB as the correct diagnosis) [2, 13].

The first priority in approaching lymphadenitis is to optimize the likelihood of microbial diagnosis. This requires that systematic cultures for mycobacteria and other pathogens be performed, as geographically appropriate, even when a diagnosis of noninfectious lymphadenopathy is favored. Ideally, one would have a presumptive diagnosis before planning management, especially when the latter entails surgical resection. In some practice settings, the TST may do the trick in this regard [10], but in many others, it would prove to be unreliable.

There are other concerns about the generalizability and validity of the conclusions reached by Lindeboom et al. [10]. They studied a relatively homogeneous group of children and adolescents (mean age, 4 years), “all in good health” and lifelong residents of a low-risk country for TB, who were tested serologically for alternative diagnoses. Further evidence would be needed to extend their TST strategy to adults, more diverse populations, and patients with systemic illness. As the authors acknowledge, referral bias probably skewed their assessment of skin test performance. NTM accounted for 64% of all diagnoses, resulting in a high positive predictive value that likely overestimates that which is applicable to the general population. The ratio of NTM to TB cases, 112:1, is probably unrepresentative of most populations. This ratio ranged from 11:1 to <1:1 in series from the prior 3 decades [2, 5, 9], when TB was more prevalent. There was no formal assessment of anergy in the study cohort. Anergy, although uncommon in this setting, would reduce skin test sensitivity in patients with mycobacterial infection. Conversely, anergy in the non-NTM control group might falsely inflate the specificity; a high specificity is crucial to the TST’s proposed screening role.

As more effective drug regimens for now-difficult NTM infections are developed, there will be an increasing premium on accurate microbial diagnosis and possibly on drug susceptibility testing. The therapeutic role of surgery may decline, as has already occurred in TB lymphadenitis. Our reliance on skin tests, with their troublesome cross-reactivity, may also wane as more specific tests of immune responsiveness, like the new IFN-γ assays for *M. tuberculosis* infection, become clinically available. The development of similar tests
for MAC and other common NTM could render a purified protein derivative–based strategy obsolete, at least for health care systems that can afford them. For much of the world, the TST will remain a practicable, albeit problematic, aid in recognizing mycobacterial infection.

In conclusion, Lindeboom et al. [10] provide valuable data on an important clinical problem, but their proposed use of tuberculin reactivity to identify children with NTM lymphadenitis lacks general applicability and may prove controversial. Given careful heed to the clinical and epidemiologic caveats, their strategy could help to manage selected cases efficiently. Their report reminds us that, as with politics, all clinical mycobacteriology is local.

References