Cervical Lymphadenitis Caused by Atypical Mycobacteria

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Mycobacteria can cause a variety of human diseases, of which tuberculosis is the most familiar to clinicians in this country. Tuberculosis is caused by the organisms *M. tuberculosis* and *M. bovis,* or by *M. africanum* as reported from only the western coast of Africa. Although uncommon in the USA, leprosy is prevalent in other parts of the world and is caused by *M. leprae.* Atypical mycobacteria can generally be thought of as mycobacteria other than the species named above. The term "atypical" was first used in the 1950s when it was apparent that some mycobacterial isolates from clinical specimens were neither *M. tuberculosis* nor *M. bovis.* Other descriptive terms have included "anonymous" or "unclassified" but these terms are now inappropriate, since the mycobacteria have been given species names, and serotypes have been described for some. "Opportunistic" had been suggested as a term, because a predisposing condition was felt necessary for disease to occur in humans. Although this may be true for some adult pulmonary diseases, it does not account for most pediatric infections. Also, the names mycobacteria other than tuberculosis (MOTT) and nontuberculous mycobacteria (NTM) have been suggested. However, the term atypical is used in the this article because it is more commonly recognized by clinicians, and infections from these organisms differ in pathogenesis and treatment from those caused by *M. tuberculosis.* In addition, the literature concerning these infections is listed in the *Index Medicus* under the subject-heading "Mycobacterium Infections, Atypical".

The anatomic sites commonly affected by these organisms differ in adults and children. Usually, adults have chronic pulmonary infections, whereas children have chronic lymph node infections. The specific topic of this article is lymph node infections in children that occur in the neck and face. However, infections have also been reported in axillary, epitrochlear, and inguinal nodes. In addition, skin, soft tissue, skeletal, lung, genitourinary, meningeal, and disseminated infections have occurred.

Descriptive Terminology

Approximately 20 years ago, Runyon proposed a preliminary classification of atypical mycobacteria that was based on growth characteristics and the ability to form pigment. This classification includes four groups. Group I, the photochromogens, do not produce pigment if grown in the dark but become bright yellow after exposure to light. Group II, the scotochromogens, produce a bright orange pigment whether grown in the light or dark. Group III, the nonphotochromogens, do not produce pigment when grown either in the light or dark. Group IV, the rapid growers, produce visible growth within several days. (Most mycobacteria require several weeks to produce visible colonies.) Currently, these mycobacteria are more precisely identified by species names, such as *M. scrofulaceum,* although most species generally fit into one of Runyon's original groups.

Epidemiologic Aspects

Atypical mycobacteria are frequently found in soil, water, milk, and house dust; they can also be isolated from domestic and wild animals, and from birds. Some studies preceded species identification and, therefore, the isoltaes were described only by the Runyon group. It is now known, however, that all species within each group are not pathogenic for humans. For example, both *M. scrofulaceum* and *M. gordonae* can be categorized as Runyon Group II. Although *M. gordonae* have been recovered from soil, they are unlikely to be recovered from clinical speciments such as pus that has been obtained from infected lymph nodes.

Chapman isolated atypical mycobacteria of Groups II, III, and IV from raw and pasteurized milk, and found that the number of isolates obtained in winter was greater than that found in spring and summer. Similar seasonal variations were found in isolations from human material. In another study, the majority of children with cervical lymphadenopathy from atypical mycobacteria presented for treatment during the winter and spring.

Recognition of the large number of people apparently infected with atypical mycobacteria came with the Navy recruit skin testing studies conducted by Edwards and associates. Recruits were skin tested upon entry to the service with a standard tuberculin test (PPD-S) and also with PPD-B, which was prepared from a Battey strain of atypical mycobacteria that was isolated from a patient in the Battey State Hospital in Rome, Georgia. Of recruits who originally resided in the southeastern USA, 60 to 75 per cent had reactions to PPD-B greater than 2 mm, whereas only 17 to 24 per cent of recruits from the Northwest had similar reactions. These results show an interesting geographic variation and indicate a large number of people have been infected with some type of atypical mycobacteria.

Although disease might be expected to occur more often, some evidence indicates it is unlikely to occur even with prolonged exposure to the organisms. For example, an adult with pulmonary disease had persistently positive sputum for *M. scrofulaceum,* and none of his children became infected. Also, atypical mycobacterial lymphadenitis has been reported infrequently in the same family. Only five pairs of siblings were found in Lincoln's review of 477 cases of adenitis, and it was felt that their infections could be related to a common source rather than to familial spread. Furthermore, lymphadenitis rarely progresses to widespread disease. Disseminated disease has been reported, but these children have usually presented with widespread disease when first seen. Also, they often had preexisting diseases or altered immune systems. One child with cervical lymphadenopathy died a year after diagnosis with disseminated disease caused by a Group II organism identified as Gause. However, this case was peculiar because the child had been treated three years previously with isoniazid and streptomycin for pulmonary tuberculosis. Therefore, the ability of atypical mycobacteria to cause disease seems relatively limited and, in the case of lymphadenitis, the likelihood of progression to disseminated disease is remote.

Suspected Pathogenesis

Atypical mycobacterial lymphadenitis occurs predominantly in children between one and three years of age. Chapman proposed that infection may be related to ingestion of organisms in mild, and entry via skin breaks associated with eruption of the primary teeth. Although reports of oral infections can be found int he literature, they concern much older

patients. Rice reported an 18-year-old man with a retropharyngeal abscess and cervical lymphadenitis. Cultures from both sites grew mycobacteria identified as Battey bacilli. Schuit described a primary mycobacterial infection of the pharynx in a seven-year-old girl. Cultures from both the pharyngeal mass and the cervical node grew *M. intracellulare,* and biopsies from both areas showed non-caseating granulomas with acid-fast bacilli.

Clinical Presentation

Most cases of atypical mycobacterial lymphadenitis have been reported in children between one and five years of age; however, as mentioned previously, the predominant age affected is between one and three years. The disease is rare in children less than seven months, or more than 12 years, of age. The lymph nodes enlarge suddenly, but only one side of the neck or face is usually involved. The child does not appear to be sick at the time, although there may be a history of respiratory infection during the previous weeks. While some mild pain and tenderness may be present, there are no marked symptoms such as those seen with acute pyogenic infections. Several nodes often enlarge in one location and initially they may appear to be a single mass. In some cases, the mass is quite large. The enlarged nodes usually occur near the angle of the jaw, but occasionally involve the preauricular area. They are found less frequently in the submental area and along the sternocleidomastoid muscle. Supraclavicular involvement is unusual and unless associated with suspected pulmonary tuberculosis probably should indicate the need for immediate biopsy.

Early in the clinical course, the skin becomes adherent to the underlying tissues at the peripherly of the mass. Also, increased vascularity is commonly seen in the same location. Within several months, the nodes become fluctuant. (Some observers have felt that this is a more rapid evolution than is usually seen in infections with *M. tuberculosis.)* In addition, the overlying skin usually changes in color from pink to purplish-red. Although the skin appears erythematous, it is not warm to the touch. This rather distinctive color change is followed by thinning and a parchment-like appearance of the skin, and then by spontaneous drainage from the underlying node. While these skin changes and the development of fluctuation seem characteristic of mycobacterial infections, they are not specific in distinguishing atypical mycobacterial infections from those caused by *M. tuberculosis.* Also, some children develop fluctuation without any skin changes; this may erroneously suggest other diagnoses.

Diagnosis

Children of the above-mentioned ages who have chronic unilateral lymph node enlargement should be suspected of having atypical mycobacterial infections, particularly if the nodes are located around the angle of the jaw or in the preauricular area. The presence or development of characteristic skin changes and fluctuation of the mass would further support this clinical impression. The children appear healthy and there is absence of disease elsewhere in the body. Generalized lymphadenopathy and abdominal organomegaly are not found, and chest radiographs are usually normal. Also, there is no history of recent contact with an adult who has suspected or proven infection with *M. tuberculosis.*

Previously, skin test antigens prepared from various atypical mycobacteria were available from the Centers for Disease Control in Atlanta, Georgia. When tested with these antigens, children with atypical mycobacterial infections reacted to the atypical PPDs and had

larger reactions to them than to PPDs prepared from *M. tuberculosis.* Therefore, it was usually possible to distinguish between atypical mycobacterial infections and those caused by *M. tuberculosis* on the basis of the skin test reactions. Also, the skin tests were quite helpful in suggesting a mycobacterial etiology, rather than a malignant process, before skin changes or fluctuation occurred. Unfortunately, these antigens presently are not available because they are being evaluated in bioassay studies and tests of clinical usefulness.

Children with atypical mycobacterial infections may also react to standard tuberculin tests because of the cross reactivity that is known to occur. When tested with a 5 TU dose of PPD-tuberculin, these children tend to have reactions of less than 10 mm induration. (Conventionally, reactions of 10 mm or greater are believed to indicate infection with *M. tuberculosis.)* Surprisingly, a moderate number of children will have no reaction to PPD-tuberculin (5 TU). However, this lack of reactivity should not be used as a criterion to rule out the possibility of atypical mycobacterial disease. It is known that some patients infected with *M. tuberculosis* also show no reaction to conventional tuberculin tests.

Disturbingly, a few children with atypical mycobacterial infections have large reactions to PPD-tuberculin (5 TU) early in the course of their disease, and this may incorrectly suggest a diagnosis of *M. tuberculosis.* Schuit has shown that when these children are retested several months later, the size of their PPD-tuberculin reactions decreases considerably. Therefore, a child who is suspected of having an atypical infection, and whose reaction to PPD-tuberculin (5 TU) is large, should be retested several months later to see if the size of the reaction decreases.

While the above characteristics will presumptively identify children with atypical mycobacterial lymphadenitis, the only definitive proof is isolation of the infecting mycobacterium. This degree of diagnostic certainty, however, may not be necessary in all cases. Material can be obtained by needle aspiration, incision and drainage, or by surgical biopsy of the involved node. Mycobacteria require several months to grow, and in most reported series approximately one-half of the cultures that were obtained demonstrated no growth. Acid-fast bacilli may also be seen on smears from pus or in tissue sections, but the morphology of the commonly isolated atypical mycobacteria is not distinctive from the morphology of *M. tuberculosis.* Although some investigators have felt that the histopathology of atypical infections was distinguishable from infections caused by *M. tuberculosis*, Reid concluded that the features were not specific enough to enable such a differentiation.

Treatment

The predominant species of mycobacteria isolated from cervical lymph nodes have been either *M. scrophulaceum* or members of the *M. avium-intracellulare* complex (Runyon Groups II and III respectively). Both show marked resistance in vitro to the usual antimycobacterial drugs. Early reports from Dallas, Texas mentioned the frequent isolation of *M. kansasii* (Runyon Group I). While this species may respond to rifampin, the number of *M. kansasii* isolates in Dallas has decreased markedly in recent years for unknown reasons, and *M. kansasii* have been reported infrequently in other series. Because of the factors of drug resistance of the common species, the low risk of human-to-human spread, and the remove

chance of dissemination, antimycobacterial drugs are felt to be unnecessary. Good results without the use of such drugs have been reported by several investigators.

Surgical therapy of these infections has included needle aspiration, incision and drainage, incision and curettage, and total excision. A recent review of the management of atypical mycobacterial lymphadenitis favors total excision, but we believe that an alternative "nonexcisional" approach, which will be described later, has some advantages.

Long-Term Effects

Most children with atypical mycobacterial infections have not been followed for long periods of time, and therefore the development of late sequelae, such as recrudescence in adult life, is unknown. One problem has occurred, however, when these children are tuberculin-tested at the time of entering school. Their previous atypical mycobacterial infections are often forgotten, and because of cross reactivity to the tuberculin test, they are mistakenly thought to have tuberculosis.

Pittsburgh Experience

From 1967 to the present, the author has seen major children from this geographic area who were suspected of having atypical mycobacterial lymphadenitis. Of these children, a group with the following characteristics was selected. The location of the node was in the neck or face; the culture was positive for either *M. scrofulaceum* or members of the *M. avium-intracellulare* complex; the results of skin tests with atypical antigens were available; and the children resided in the western Pennsylvania area. Twenty-seven children satisfied all four conditions and these children had not been previously reported.

During the same period, two additional children were seen who had similar species of atypical mycobacteria isolated from a different location. Both had inguinal node infections, one from *M. scrofulaceum* and the other from *M. avium-intracellulare* complex. Two other children had cervical nodes from which *M. fortuitum* was isolated. This organism is usually associated with injections or trauma, and in one case it was known that the child was cut in the face by an exploding soft-drink bottle. Because of the pathogenesis of *M. fortuitum* appears to be different, both of these children were excluded from this report. Also, no isolates of *M. kansasii* were obtained from nodes in any location.

The infections usually involved a group of nodes in only one anatomic location. The cervical group of nodes, ie, those near the angle of the jaw and the submandibular area, were most commonly affected. In five children, however, both the cervical and the preauricular nodes were involved. Except for one child, all infections were unilateral. There was mote consistency in the locations associated with *M. scrofulaceum* infections that those caused by the *M. avium-intracellulare* complex. Infections in nodes along the mid-to-lower portions of the sternocleidomastoid muscle and in the submental area were found only with the latter species.

The ages are given in terms of estimated onset of the enlarged nodes as determined by history. Most infections had their onset in children between one and three years of age (67

per cent). The youngest child was 13 months, the oldest 10 years, 7 months. Almost equal numbers of males and females were affected, but considerably more infections were seen in white children. In the majority of children, the onset was during the first six months of the year. This seasonal variation was most apparent with the *M. scrofulaceum* isolates.

All 27 children were skin tested with a 5 TU dose of PPD-B, G, and Y. (These antigens were originally supplied by the Centers for Disease Control in Atlanta, Georgia.) All children reacted to one or more of the tests, and the mean sizes of the reactions in terms of induration were 13 mm, 14 mm, and 8 mm, respectively. Twenty-five children were simultaneously tested with PPD-tuberculin (5 TU). In all 25 patients, the degree of induration from one of the atypical PPD tests exceeded the PPD-tuberculin by at least 6 mm. (The atypical tests do not distinguish among the various species of atypical mycobacteria.) However, in 13 children (52 per cent) there was no induration to PPD-tuberculin. If these children had not been tested with the atypical skin tests, it may have been falsely assumed that they did not have a mycobacterial infection. Some referring physicians mentioned that their patients had reactions to tuberculin screeing tests and more recently we have added a Tine test. In five children recently seen with positive cultures who had no induration to PPD-tuberculin, the Tine test caused some induration in all of them. The reactions were usually small (1 to 2 mm) but there was definite induration. Therefore, in the absence of atypical PPD skin tests, the dual use of a Tine test and PPD-tuberculin may be more helpful in suggesting a diagnosis of an atypical mycobacterial infection. (Whether other screening tests would work equally well is unknown.)

The total duration of these infections varies from approximately 9 to 15 months. Generally, the skin changes occur within the first several months. Initially, the border of the mass becomes pink and an increased number of small blood vessels appear at the periphery. As the color progresses to a characteristic purplish-red, the skin develops a parchment-like appearance and begins to peel. The node is usually fluctuant at this time and spontaneous drainage may occur. Early in the course, the skin becomes attached to the outer edges of the node, and the dimpling of the skin that occurs later is most likely related to this early inflammatory response. If the node spontaneously ruptures, or if surgical drainage is performed, there may be continued drainage for a period of months. The enlarged node then gradually regresses and the opening in the skin closes over. Finally, the skin color returns to normal.

Although the literature suggests that these nodes should be excised, we have found other approaches to be satisfactory. Because of the chronic inflammation, the nodes are densely adherent to the surrounding tissues, and therefore dissection is quite difficult. Injury to the mandibular branch of the facial nerve can occur following surgical excision; in one series, skin breakdown followed the excision of preauricular nodes in two of five children. Once the skin is involved, a moderate sized area of excision may be necessary, and it is not surpirising that breakdown occurs, particularly in the preauricular area. The "nonexcisional" methods that have been used include needle aspiration, incision and drainage, and incision and curettage. The specific method chosen depends on the stage of the disease and the extent of the fluctuant area. We feel it is safer to revise the scar and skin contracture later, if necessary, rather than to widely excise the lesion and risk a problem of skin breakdown or facial nerve injury, even though these risks are relatively small. Also, these children have not been treated with antituberculous drugs unless the diagnosis was uncertain initially.

Of the 27 children reported here, only six had other surgical procedures. Five children had biopsies and one child had a partial excision of her mass. In all six, another disease (usually malignant) was suspected preoperatively, and in five, skin testing with atypical PPDs had not yet been performed. Skin testing was suggestive of atypical mycobacterial disease in the sixth child, but because the mass had not regressed, a biopsy was performed.

No known complications have resulted from this nonexcisional approach. In some children, however, drainage from the affected nodes has persisted for two to four months. The parents and children have accepted this prolonged course when it is explained that the drainage is not contagious and that the lesion will eventually heal. Photographs of other children with healed lesions have been used to illustrate the end results. Interestingly, nonexcisional procedures such as incision and manual expression of the pus, or incision with enzyme treatment, had been proposed in the past to treat tuberculous lymphadenitis caused by *M. tuberculosis.*

Dissemination of disease following lymph node infections has not been observed. Two cases, however, occurred in one family. A younger sister had a partial excision for a suspected parotid tumor and within two months her older brother developed an infection on the same side of his neck. *M. scrofulaceum* was obtained from the cultures of both children. In another child a mass developed in the same location six years after her infection with *M. scrofulaceum.* A recurrent mycobacterial infection was suspected but never proven. The surgeon described the node as acutely inflamed, but cultures for bacteria (including anaerobic organisms), yeast, fungi, and mycobacteria were sterile. The histopathologic findings were interpreted as chronic inflammation. Interestingly, a radiograph of the patient's neck showed bilateral calcification of the nodes at the time of readmission. The calcification was more marked on the left side, which was the site of the original infection.

During this same 13 year period, there were no isolates of *M. tuberculosis* from nodes in the neck and face as determined from review of the bacteriology records at Children's Hospital of Pittsburgh. However, *M. tuberculosis* was recovered from an inguinal node of one child and an axillary node of another. These results vary considerable from a study in North Carolina where *M. tuberculosis* was recovered from a large number of children.

Factors to consider in the differential diagnosis of chronic unilateral cervical lymphadenitis in the anatomic locations described previously vary depending on the local experience. In our area, the factors primarily include atypical mycobacteria, malignant disease, and nonspecific lymphadenopathy. In other areas, infections with *M. tuberculosis* should be included. Unfortunately, it was easier to distinguish between infections from atypical mycobacteria and those from *M. tuberculosis* when skin tests for atypical mycobacteria were available. Hopefully, these antigens will again be available in the USA.

Summary

Atypical mycobacterial lymphadenitis is basically a benign disease. Although children between one and five years of age are commonly affected, the predominant occurrence is in those from one to three years old. The children are frequently brought to the physician because of chronic unilateral lymph node enlargement. Most often, the nodes are located near

the angle of the jaw, but they may also be found in the preauricular area. The overlying skin usually becomes discolored within several months of onset, and the nodes become fluctuant. Some data are available to support the hypothesis that a primary oral source is responsible for these infections. Mycobacteria identified as *M. scrofulaceum* and those belonging to the *M. avium-intracellulare* complex are the common species that have been isolated from infected nodes. Infections tend to occur more frequently during the first six months of the year.

Although currently not available, atypical PPD skin tests were useful in distinguishing atypical mycobacterial infections from those caused by *M. tuberculosis.* These skin tests were also quite helpful in suggesting a mycobacterial infection, rather than a malignant process, before skin changes occurred or the nodes become fluctuant. Skin tests with standard PPD-tuberculin (5 TU) may result in intermediate sized reactions, ie, less than 10 mm of induration. However, some children with culture-proven atypical mycobacterial infections either have no reactions, or large reactions, to the same tests.

Because of the low risk of communicability, in vitro drug resistance of the commonly isolated species, and the unlikelihood of spread within the host, antimycrobial drugs are not required to treat these infections. Although the literature favors surgical excision of the infected nodes, an alternative nonexcisional approach has some advantages and seems to provide good long-term results.

Finally, it is important to remind parents that children who have such infections may react to tuberculin tests later in life. This is particularly important in order to prevent unnecessary concern or inappropriate treatment for suspected tuberculosis, when these children are tuberculin-tested at the time of school entry.