

# Mycobacterial Cervical Lymphadenitis

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## Key Words

Mycobacterium tuberculosis · Atypical mycobacteria · Lymphadenitis

## Abstract

Cervical lymphadenitis is the most common head and neck manifestation of mycobacterial infections. The incidence of mycobacterial cervical lymphadenitis has increased. It may be the manifestation of a systemic tuberculous disease or a unique clinical entity localized to neck. It remains a diagnostic and therapeutic challenge because it mimics other pathologic processes and yields inconsistent physical and laboratory findings. A high index of suspicion is needed for the diagnosis of mycobacterial cervical lymphadenitis. A unilateral single or multiple painless lump, mostly located in posterior cervical or supraclavicular region can occur. A thorough history and physical examination, tuberculin test, staining for acid-fast bacilli, radiologic examination, fine-needle aspiration and PCR will be instrumental in arriving at an early diagnosis early institution of treatment before a final diagnosis can be made by biopsy and culture. It is important to differentiate tuberculous from nontuberculous mycobacterial cervical lymphadenitis because their treatment protocols are different. Tuberculous adenitis is best treated as a systemic disease with antituberculosis medication. Atypical infections can be addressed as local infections and are amenable to surgical therapy.

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## Introduction

The term acid-fast bacilli is practically synonymous with mycobacteria. Mycobacterial species with similar bacteriologic features and DNA are referred to as ‘complex’, like *M. tuberculosis complex* and *M. avium complex*. The former includes *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. ulcerans* and Bacille Calmette-Guérin (BCG). Mycobacteria that are not classified as *M. tuberculosis complex* are referred to as nontuberculous mycobacteria (NTM) or atypical mycobacteria.

The tuberculous bacilli that cause disease in humans are usually *M. tuberculosis*, *M. bovis* and *M. africanum*. The latter two mostly cause extrapulmonary tuberculosis. Humans are the only reservoir for *M. tuberculosis*. In general, mycobacterial infections are grouped into infections caused by *M. tuberculosis* and those caused by the atypical mycobacterial organisms [1].

Primary infections mostly occur by contamination through the respiratory tract. Reinfection can occur any time after the primary infection either through reactivation of the endogenous source of primary infection, or contamination by an exogenous source. Miliary tuberculosis occurs when a caseating focus drains into a vessel and disseminates into the circulation. The age distribution reflects the degree of ongoing transmission in a given population. Disease in the elderly is generally due to reactivation of infection acquired in the remote past, whereas tuberculosis in young children indicates ongoing active transmission in the community.

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**Table 1.** Clinical clues to differentiate between tuberculous and nontuberculous cervical adenitis

Parameter	Tuberculous	Nontuberculous
Cervical lymphadenitis	Posterior, supraclavicular, multiple, bilateral	Enlarging mass around the mandible
Constitutional symptoms (fever, weight loss, fatigue)	Present	Absent
History of tuberculosis or tuberculous contact	Present	Absent
Fistula formation	High	Low
Age	Adulthood	Childhood
PPD	Usually positive	Intermediate, negative
Chest X-ray	Signs of active or previous tuberculous infection	Normal

Cervical lymphadenitis is the most common manifestation of mycobacterial infections encountered in the otolaryngologic practice. The incidence of mycobacterial cervical lymphadenitis has increased in parallel with the increase in the incidence of mycobacterial infection worldwide. Mycobacterial cervical lymphadenitis, which is also referred to as scrofula, may be manifestation of a systemic tuberculous disease or a unique clinical entity localized to neck. It can result from direct extension or hematogenous spread of the infection [2]. Mycobacterial cervical lymphadenitis remains a diagnostic and therapeutic challenge because it mimics other pathologic processes and yields inconsistent physical and laboratory findings [3].

### Clinical Presentation

Mycobacterial infection should be considered in the differential diagnosis of a cervical mass, especially in endemic areas. Lymphadenitis is the most common clinical presentation of extrapulmonary tuberculosis [4]. It may present as a unilateral single or multiple painless lump, mostly located in the posterior cervical or supraclavicular region [2, 5]. There is a history of tuberculous contact in 21.8%, and tuberculous infection in 16.1% of the cases [2]. Fistula formation can be seen in almost 10% of the mycobacterial cervical lymphadenitis [2, 6], though it is rare in atypical cases [7].

Cervical adenitis due to NTM is primarily a disease of childhood, and usually presents as a unilateral mass or draining sinus [8, 9]. Cervical nodes in the submandibular region are most commonly affected in children [10, 11]. Children below 3 significantly more often present with only one lesion and the referring physician more frequent-

ly suspects a neoplasm, bacterial adenitis or reactive adenopathy rather than nontuberculous mycobacterial cervical lymphadenitis [12]. The portal of entry for NTM may be the oral mucosa or gingiva [13]. This is particularly important in children, because deciduous teeth may harbor the NTM that may reach the neck sites around the mandible through the lymphatics [2].

### Diagnosis

A high index of suspicion is needed for the diagnosis of mycobacterial cervical lymphadenitis, which remains a diagnostic challenge for many clinicians despite current advances in diagnostic laboratory techniques.

A thorough history and physical examination, tuberculin test, staining for acid-fast bacilli, radiologic examination, and fine-needle aspiration (FNA) will help to arrive at an early diagnosis of mycobacterial cervical lymphadenitis which will allow early institution of treatment before a final diagnosis can be made by biopsy and culture [14, 15].

It is also important to differentiate tuberculous from nontuberculous mycobacterial cervical lymphadenitis because their treatment protocols are different. Although it is difficult to clinically differentiate tuberculous from nontuberculous lymphadenitis [16], there are some clues that may be used in their differentiation (table 1).

#### Smears

Smears can be obtained either from a draining sinus or by FNA. Ziehl-Neelsen staining of the smears may reveal mycobacteria in the fresh specimens; and 10,000 cells are needed for smear positivity.

FNA cytology is useful in the diagnosis of tuberculous and nontuberculous adenitis [16–18]. It can detect cervical tuberculous lymphadenitis in 25–77% [19–22]. In NTM, acid- and alcohol-fast bacilli can be identified in 52.9% [23]. The sensitivity and specificity of FNA cytology in the diagnosis of tuberculous lymphadenitis are 88% and 96%, respectively [16]. Combination of FNA with culture or a Mantoux test further increases the diagnostic yield in mycobacterial cervical lymphadenitis [22, 24, 25].

FNA biopsy is a sensitive, specific and cost-effective way to diagnose mycobacterial cervical lymphadenitis [20], especially in children presenting with a suspicious neck mass [26].

### Culture

Culture of mycobacterium is diagnostic for mycobacterial cervical lymphadenitis. However, a negative culture result should not exclude the diagnosis of mycobacterial cervical lymphadenitis [27]. The presence of 10–100 bacilli per cubic millimeter of the specimen is enough for a positive culture result. Different media can be used to culture the mycobacteria (L-J, Petregani, Trudeau, Middlebrook, Bactec TB). However, several weeks are needed to obtain the culture result, which may prolong the initiation of treatment.

Cultures are positive in 10–69% of the cases [2, 19, 28]. Mycobacterial cervical lymphadenitis is caused by tuberculous mycobacteria in 64% and nontuberculous mycobacteria in 36% of the cases [2]. In tuberculous adenitis, *M. tuberculosis* is the most common causative agent (cultured in 50%), followed by *M. bovis* [14, 28]. In nontuberculous adenitis, *M. avium-intracellulare complex* is the most common causative agent [11, 24, 29, 30], and can be cultured in 68.8% of the cases [23]. It is a common causative agent of mycobacterial cervical lymphadenitis in children less than 3 years [31]. *M. kansasii* and *M. fortuitum* are rare causes [28].

### Tuberculin Test

This intradermal test (Mantoux test) is used to show delayed-type hypersensitivity reactions against mycobacterial antigen, in which the reagent is mostly protein purified derivative (PPD). The test becomes positive 2–10 weeks after the mycobacterial infection. Positive reactions (>10-mm induration) can occur in *M. tuberculosis* infections. Ninety percent of persons with 10-mm and all with >15-mm of indurations are infected with *M. tuberculosis*. Suspicious reactions (5- to 9-mm induration) can occur after BCG vaccination, *M. tuberculosis* infection or

nontuberculous mycobacterial infections. Negative reactions (<4-mm induration) represent a lack of tuberculin sensitization. False-negative reactions can occur in at least 20% of all persons with active tuberculosis. The test may also be false positive in different conditions, like other infections, metabolic disease, malnutrition, live virus vaccination, malignancy, immunosuppressive drugs, newborns, elderly people, stress, sarcoidosis and inadequate test application.

The tuberculin test is considered the principal diagnostic tool in mycobacterial infections [32, 33], though its value is debated [22, 23]. Children with atypical mycobacterial adenitis have a decreasing tuberculin response to repeated testing, while children with tuberculous adenitis have a stable response [34]. In mycobacterial cervical lymphadenitis cases the test may be positive (49.4%), intermediate (35.6%) or negative (15%) [2]. Positive results could be obtained in the majority of tuberculous infections whereas the result is mostly negative or intermediate in nontuberculous infections.

### Molecular Testing

PCR testing, especially IS6110 profile, is a fast and useful technique for the demonstration of mycobacterial DNA fragments in patients with clinically suspected mycobacterial cervical lymphadenitis [35, 36]. The presence of 10 microorganisms is enough for PCR positivity. PCR can be applied on the materials obtained by FNA or biopsy, and can reduce the necessity for open biopsy [37, 38]. Its sensitivity ranges between 43 and 84%, and its specificity between 75 and 100% [36, 39]. PCR can be applied when smears and cultures are negative [40].

PCR is a confirmatory and sensitive technique for the diagnosis of mycobacterial cervical lymphadenitis. However, different PCR results can be obtained in different laboratories. Therefore, PCR is used as an adjunct to conventional techniques in the diagnosis of mycobacterial infections [39, 38].

### Histopathology

Histopathologic examination is one of the most important means for diagnosing mycobacterial cervical lymphadenitis [3, 29, 41–43]. Langerhans giant cells, caseating necrosis, granulomatous inflammation and calcification can be seen [44]. The presence of microabscesses, ill-defined granulomas, noncaseating granulomas and a small number of giant cells is more prominent in nontuberculous adenitis when compared with tuberculous adenitis [9, 23, 45].

### *Radiology*

Chest roentgenogram, and ultrasound, CT and MRI of the neck can be performed in mycobacterial cervical lymphadenitis. Chest X-ray may reveal findings consistent with tuberculosis in 14–20% of the cases [2, 3, 14]. The majority of them are tuberculous infections. Chest X-ray is usually clear in nontuberculous infections [23]. Ultrasound of the neck can demonstrate singular or multiple hypoechoic and multiloculated cystic lesions that are surrounded with a thick capsule.

On CT, the presence of conglomerated nodal masses with central lucency, a thick irregular rim of contrast enhancement and inner nodularity, a varying degree of homogeneous enhancement in smaller nodes, dermal and subcutaneous manifestations of inflammation, such as thickening of the overlying skin, engorgement of the lymphatics and thickening of the adjacent muscles, and a diffusely effaced fascial plane may suggest mycobacterial cervical lymphadenitis [46, 47]. However, these findings may also be seen in other diseases like lymphoma and metastatic lymphadenopathy [46]. With gadolinium enhancement, there will be opacification around the hypodense cystic lesions.

MRI may reveal discrete, matted and confluent masses. Necrotic foci, when present, are more frequently peripheral rather than central, and this together with the soft tissue edema may be of value in differentiating mycobacterial cervical lymphadenitis from metastatic nodes [48]. If the cervical mass is necrotic, there will be low and high signal intensity in the center of the mass in T<sub>1</sub>- and T<sub>2</sub>-weighted images, respectively.

### **Treatment**

It is important to distinguish between tuberculous and nontuberculous cervical lymphadenitis because the medical and surgical treatments of these entities differ [49, 50]. A tuberculous infection usually responds very well to antituberculous chemotherapy, whereas a nontuberculous mycobacterial infection may require a surgical intervention [51, 52].

Tuberculous adenitis responds well to antituberculous drugs, and surgery has a limited role in the treatment. A surgical intervention in tuberculous adenitis should include FNA, drainage, and incisional or limited excisional biopsy [53].

In nontuberculous adenitis, surgery is the treatment of choice: it provides a rapid tissue diagnosis and confirms the bacterial type [54, 55]. Surgery increases the cure rate

with excellent cosmetic result and a low complication rate [56]. Antibiotics are used to augment surgical therapy [15].

Surgical techniques include aspiration, incision and drainage, curettage, complete surgical excision of the affected lymph nodes and the overlying skin, and selective nodal or functional neck dissection when required. Briefly, the treatment of choice is complete surgical excision of all affected tissue [11]. Aspiration, which may result in 50% cure rate, can be performed when surgical excision is limited because of the proximity of adenitis to the facial nerve or its branch [57]. Curettage, which may result in 70% cure rate, can also be made when the lesion is in proximity to the nerve or there is extensive skin necrosis [17, 58]. Simple incision and drainage are associated with prolonged postoperative wound discharge and hypertrophic scarring [59]. Total excision is made for a singular lump while selective nodal or functional neck dissection for multiple lumps. In nontuberculous adenitis, the recurrence rate of complete surgical resection is less than 1% [60]. Excision of the skin overlying the mass can be performed when there is a fistula, scar formation, or necrosis. Dilated lymphatics can be seen around the lymphadenitis during surgery, which should be secured to prevent the formation of a chylous fistula postoperatively.

Medical treatment for mycobacterial cervical lymphadenitis includes antibiotics, which are used in combinations in order to sterilize the infectious focus and to prevent the development of drug resistance. There are two groups of antituberculous drugs. First-line drugs are isoniazid (INH), rifampin (RMB), ethambutol (EMB), pyrazinamide (PZA) and streptomycin (STM). Second-line drugs, which are less efficacious and more toxic than the first-line drugs, are capreomycin, kanamycin, ethionamide, thiacetazone, para-aminosalicylic acid and cycloserine. INH may be hepatotoxic, RMB and PZA may cause hepatorenal disorders, STM may be ototoxic and nephrotoxic. EMB may cause optic neuritis. Resistance to one or more drugs is seen in 61% of isolated strains with maximum resistance to INH and minimum to EMB [61]. Treatment should not be deferred during pregnancy. If there is a contraindication, multiple puncturing, aspiration and compressive dressing can be made until termination of the pregnancy. Otherwise, INH and EMB can be used in drug-sensitive cases. RMP can also be used when a 9-month regimen is advocated. STM and PZA are not recommended during pregnancy. A biopsy can be obtained under local anesthesia during pregnancy. However, complete surgical excision under general anesthesia can be performed after the second trimester.

There is no standard regimen for the medical treatment of mycobacterial cervical lymphadenitis. For tuberculous adenitis, there are treatment schedules of 6 and 9 months duration, which have similar relapse rates of 3.3 and 2.7%, respectively [62]. In our experience, we advocate 12 and 18 months of drug treatment for tuberculous and nontuberculous mycobacterial cervical lymphadenitis, respectively, which results in complete cure after 2 years of follow-up in nearly all cases [2, 50]. The advocated regimen is as follows; (1) STM (1 g, i.m.) for 3 months with a total dose of not more than 45 g. It is given as follows; every day for the first 2 weeks, every other day for 1 month, and every 3 days for 1.5 months; (2) RIF (600 mg/day, p.o.) for 6 months; (3) INH (300 mg/day, p.o.) for 12 or 18 months; (4) EMB (900 mg/day, p.o.) for 12 or 18 months.

## Conclusion

Tuberculosis is a systemic disease, with cervical lymphadenitis of the neck being the most common extrapulmonary manifestation of the disease. Mycobacterial cervical lymphadenitis is caused either by tuberculous or nontuberculous mycobacteria. Their diagnosis and distinction need a high index of suspicion, and application of a variety of diagnostic modalities. It is not feasible or practical to apply all of the diagnostic procedures in all patients. This would be time consuming and expensive. The test battery should be individualized depending on the location of the disease and the clinical evaluation.

Tuberculous adenitis is best treated as a systemic disease with antituberculosis medication. Atypical infections can be addressed as local infections and are amenable to surgical therapy.

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