Chapter 4

Peripheral Tuberculous Lymphadenitis: Clinical Approach and Medico-Surgical Management

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Abstract

Tuberculosis stays unique; being the most common infectious disease amongst the contagious diseases around the world, even though a hundred-year-old vaccination program is under way throughout most of the human population. Peripheral tuberculous lymphadenitis is met as the second common entity following lung infection. In this chapter, the innumerous presenting clinical features and the diagnostic workout, solution of diagnostic challenges, the timing and indications of operative intervention in peripheral tuberculous lymphadenitis will be reviewed, with regards to contemporary literature and personal experience covering medical and surgical expertise.

Introduction

Tuberculosis possesses a heavy bulk of morbidity amongst the infectious diseases. The preventive approach is best carried out by strict control of the contagious source, active immunization during early childhood and chemoprophylaxis after inevitable contact with the untreated patient. Bacillé Calmette-Guerin vaccine is the sole vaccine in use against tuberculosis. Since its first application in humans in 1921, it has shown only modest protective effect, covering approximately 50% against all forms of the disease [1].
Epidemiology

Tuberculosis related disease referral to a therapeutic care center usually contains a pulmonary involvement. In the pediatric age, however, infection due to extrapulmonary presentation is common. By a precision based definition, extra-thoracic (excluding tuberculous lung and/or pleural disease and mediastinal lymphadenopathy) infection in children covers more than one-third to a nearly one-half of the presenting cases [2]. Peripheral tuberculous lymphadenitis (TLA), primarily affecting the cervical anatomy is the most frequent form of extra-thoracic tuberculosis in children [3]. History of close contact with a patient suffering from active tuberculosis is present in some of the cases. Meticulous investigation of the family and population in close proximity is mandatory in such patients. The affected children may present at any age. Adolescents are affected slightly more frequently [4] and the younger ones being more often susceptible to atypical mycobacteria [5].
Etiology

Tuberculosis is an infectious disease of the *Mycobacterium tuberculosis* complex, making up a group of closely resembling microorganisms: *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti*, and *Mycobacterium canetti*. This group shares the common features of other mycobacteria: modelling a nonmotile, non-spore-forming, slow-growing, pleomorphic slender and slightly “bent” rod, measuring 1 to 5 μm (Figure 1). High content lipid component is basically the characteristic composition of the cell wall. This “waxy capsule” enables endurance against the sunlight,
the changes in environmental pH, and supports durability to bactericidal action of antibodies and complements. As well as all mycobacteria, they cannot be decolorized even with high concentration of alcohol and hydrochloric acid after treating with certain dyes (specifically, carbol fuchsin, crystal violet and auramine), giving them an outstanding property of acid-fastness. These pathogens cannot be differentiated, based solely on clinical features or routine laboratory tests. A distinction amongst *M. bovis* from *M. tuberculosis* is specifically essential, since the epidemiology, treatment, and prevention are different.

Nontuberculous mycobacteria may also cause peripheral lymphadenitis, especially in those suffering from human immunodeficiency virus (HIV) co-infection [6]. They are ubiquitous in the environment and are found in water, food, soil and animals.

**Clinical Presentation**

Tuberculous lymphadenitis usually develops within several weeks to several months of acquisition of microorganism. Bacilli may gain access through the alimentary tract, following airborne inoculation into alveoli, or less commonly via contagious contact from an open wound. The spread may mainly be via lymphatics to peripheral lymph nodes, or rarely by hematogenous dissemination (thus resulting in generalized lymphadenopathy). TLA
differs from an ordinary suppurative lymphadenitis with a prolonged duration of inflammation process, lasting from weeks to months. An eventual lymphoid hyperplasia is followed by the development of a granuloma. The early presentation will be a painless, matting mass closely adherent to the neighboring tissue and the overlying skin without discoloration, local endurance or fluctuation. Nearby lymph nodes are usually involved. The prominent node is asymmetrically enlarged, evolving very slowly into a necrotic caseation [7].

Despite proper medication, the mass will likely progress into a form of liquefaction in some patients, and will endure for months referred to as the “cold-abscess” (Figure 2). In some patients, however, a preceding acute respiratory tract infection may augment this inflammation, transforming it to a modest tumor arousing pain (peri lymphadenitis) [8]. Thus, the silent clinical picture may start to evolve and develop into a classical abscess, presenting with pain, fluctuation and discoloration of the overlying skin at an unpredictable time during follow-up, eventually draining freely through a tract (Figure 3). The term scrofula, or scrofuloderma, is the classical nomination used to describe such a palpable TLA, spontaneously draining through a sinus formation (Figure 4). The term is generally attributed to cervical nodes, but may define any superficial lymph node location in the body. A persistent drainage must be expected to result for months.
Figure 2: Cold abscess of cervical lymph node due to *Mycobacterium tuberculosis* (left) and *Mycobacterium bovis* BCG (right) infection.

Figure 3: Spontaneously draining tuberculous lymphadenitis.
The most common anatomical location of peripheral TLA is the cervical region, reflecting extension from the mediastinal lymph nodes [3,4]. Presence in the supraclavicular region, on the other hand, may portray as the component of a primary complex in the upper lung area (the primary focus) [9]. Contralateral drainage of lymphatics may also result in involvement of lymph nodes on both sides.

Significant high fever and acute onset, with rapid increase in diameter of superficial nodes are unusual for clinical presentation, but may be seen in younger children [10]. A cervical unilateral, persistent (>4 weeks), nontend-

Figure 4: Subauricular location of a draining sinus ‘Scrofuloderma’. Note the previous self healed, unsightly scar located at submandibular region to the right.
er adenopathy, initially matted and getting fluctuant over time and unresponsive to antibacterials, should strongly suggest TLA and be evaluated with the use of a simple clinical algorithm especially in tuberculosis endemic setting [11]. On the other hand, it is well known that bacterial superinfection may disclose the presence of an otherwise unnoticeable tuberculous lymphadenitis. Because of this, it will be wise to prescribe a course of antibiotic pending diagnostic work-up.

**Differential Diagnosis**

History of close contact with a patient suffering from active tuberculosis is of utmost importance in differential diagnosis. Other co-morbidities that may require differential diagnosis are as follows; cat-scratch disease, tularemia, brucellosis, toxoplasmosis, certain fungal infections (histoplasmosis, coccidioidomycosis, actinomycosis), viral agents (HIV, Epstein-Barr virus, cytomegalovirus), chronic granulomatous disease, sarcoidosis, malignant transformation/metastasis (such as lymphomas, neuroblastoma, rhabdomyosarcoma, etc.), congenital remnants of the branchial cleft (branchial cyst, etc.) [12,13] and undoubtedly *M. bovis, M. bovis* related BCG and other nontuberculous mycobacterial infections.

**Diagnostic Work-Up**

A tuberculin skin test is mandatory as an initial approach, as more than half of the cases have positive reac-
tion. A chest X-ray is needed to evaluate lung parenchyma and possible presence of intrathoracic lymph nodes. An ultrasound evaluation is accessible in many institutions, and the findings may reveal high diagnostic value for cervical lymphadenitis in a tuberculosis-endemic area. It provides visualization of consistency of the mass and its relationship to surrounding structures [14,15].

Computed tomography (CT) or magnetic resonance imaging (MRI) of the mass are usually not indicated for most peripheral TLA cases. These methods are both expensive and require special technical equipment. CT has the additional disadvantage of radiation exposure to the young patient. Furthermore, MRI is insufficient to show nodal calcification, usually seen in TLA and necessitates further sonographic verification. It is wise to start with ultrasonography, then to go further with more sophisticated imaging modalities for the evaluation of any lump [16].

Definitive diagnosis of TLA is essential by means of microbiological confirmation either by molecular methods [17] or by culture, and also with histopathological workout compatible with characteristic cytomorphology [18]. Obtaining adequate specimen for bacteriological confirmation in children is a difficult issue. The main critical point of management is based on collection of proper microbiological sampling. Sample collected from the lymph node in any method should be cultured for both tuberculosis and common pyogenic agents. Fine-needle aspiration (FNA) is advocated as a minimally invasive
method, does not need sophisticated equipment to perform and can be applied in office ambient [19]. Culture has a higher positivity rate than detection of acid-fast bacilli (AFB) with direct microscopy; meaning the pathogen may still be isolated in negative AFB smears [20,21]. Biopsy obtained using FNA also enables a rapid diagnosis in pediatric mycobacterial lymphadenitis using nucleic acid amplification such as the Xpert MTB/RIF test [22]. Surgical drainage of the suppurative abscess along with the remnants of the lymph node allows obtaining material both for microbiological and histological confirmation. Finally, excisional biopsy is applied not only for diagnostic sampling but also for radical treatment. Rapid molecular epidemiologic methods such as spoligotyping, provide convenience to the caring physician with timely diagnosis of tuberculosis. A positive AFB presence under direct microscopy is mandatory in order to obtain a DNA fingerprinting by spoligotyping (Figure 5) [23].

**Figure 5:** Identification of *Mycobacterium bovis* BCG fingerprint by DNA spoligotyping.

Histologic examination is invaluable in cases with negative microbiological results [10]. The typical histopathological finding under light microscope is necrotizing or non-necrotizing granulomatous inflammation (Figure
6) [9,24]; in some series only necrosis has been identified as the most common cytopathological pattern [25]. This, however, is not pathognomonic to tuberculosis and other causative agents, such as cat-scratch disease and fungal infections should be considered.

![Image](image.png)

**Figure 6:** Caseating granulomatous inflammation on lymph node biopsy.

**Treatment**

The main objective of anti-tuberculous therapy is to prevent the dissemination of the microorganism to other organs and systems of the body. A strict protocol should be undertaken in prescribing drugs in the appropriate dosage, for an appropriate period of time, while closely
following up for possible drug toxicity. Preferred standard medical therapy is mainly composed of three or four major antituberculous agents, lasting for six months, meanwhile related to isoniazid resistance of the population. In areas with high isoniazid resistance (ie >4%), isoniazid, rifampicin, pyrazinamide, and ethambutol are included in the treatment regimen [26,27]. The patient should also be monitored in terms of normal growth and development, as well as the size, consistency and active drainage of the existing lymph node. Systemic workout of the remaining body parts, for concomitant node enlargement is very important. It should be kept in mind that the size of the infected lymph node will not return to its original size rapidly.

Exacerbation of lymph nodes even under appropriate medications is a well-known outcome of antituberculosis therapy, a state called immune reconstitution inflammatory syndrome (IRIS). This paradoxical reaction is self-limited and does not mean failure (Figure 7). Close follow-up of the patient, reevaluation for any resistant infection and most importantly, good adherence to therapy is mandatory in decision making management.

The larger the node initially, the more prominent is the enlargement under therapy, which in turn may increase the need for surgical intervention [28]. As TLA with resistant strain will not respond to empirical therapy, this will also necessitate surgical intervention for obtaining microbiological sampling at the onset of anti-tuberculous regimen.
There is considerable argument about the modality and timing of surgical management [8,9]. The decision making of surgical approach in TLA needs sufficient clinical expertise, and a high index of suspicion, mostly acquired during close follow-up of its various clinical presentations. Delayed presentation is common, possibly due to most of the patients’ low income and admission from rural areas [29].

During the suppurative stage, whether presenting with spontaneous drainage or not, a simple incision and drain-
age is advocated in the office ambient. The aim should be to drain as much as possible, since a persistent drainage may only be avoided where one can extirpate the abscess totally along with its surrounding capsule, which may be possible especially in cases with axillar adenitis. At best the drainage material will be composed of pus and caseification necrosis. Be sure to send the material separately for bacterial and histopathological examination. In terms of total extirpation of the surrounding capsule, the wound is expected to heal spontaneously within days. A draining sinus tract after rupture of caseating lymph node is usually resistant to spontaneous healing, further necessitating surgical removal (Figure 8). A second operative intervention and an excisional biopsy in the operating room is indicated, in case of failure in total extirpation [30]. Such an attempt should be delayed until the local inflammation is at best under control.

Non-tuberculous mycobacterial adenitis is usually treated by excisional biopsy [31,32]. Surgical approach under general anesthesia is mainly based on diagnostic origin but may be curative as well. Most publications have underlined the fact as to where intervention should be individualized depending on the location of the disease and the clinical evaluation [7]. Even though an attempt to excise all involved lymph nodes is not advocated, we believe that the patient will benefit from removing all available enlarged nodes with no drain left in place [33]. In presence of a fistula, scar formation, or necrosis, excision of
the skin overlying the mass may result in better cosmesis, preventing further fistula formation. Submandibular location carries the risk of injury to the branches of facial nerve; however, a resulting paresis is mostly expected to be transient. In such patients when the lesion is in proximity to the nerve or there is extensive skin necrosis, drainage and curettage alone is reported to result in 70% cure rate, and the rest resulting in sinus formation [34]. Finally, FNA of the relevant node requires no sophisticated equipment to perform [30], but a resultant draining sinus tract usually resistant to spontaneous healing, further forming unsightly cheloids will promote surgical removal [29].

Figure 8: Draining sinus tract of tuberculous cervical lymphadenitis.
High possibility of a chronic draining sinus and formation of an unpleasant scar, or need for an eventual surgical biopsy following insufficient drainage, render the modality and timing of surgical management critical. The advantages of early surgical treatment are rapid healing, low recurrence rate and reduced hospital stay [8]. We believe that, the best result will be obtained via an excisional lymphadenoidectomy accompanying the overlying skin using proper surgical manipulation, where adequate biopsy material with culture may be obtained for etiologic work-up, leaving a good cosmetic result, with a low complication rate.

A detailed immunological work-up, including assays surveying Mendelian susceptibility to mycobacterial disease (MSMD) is required in patients, with non-tuberculous mycobacteria (primarily *M. bovis* BCG) isolated from an axillary lymph node. Since significant differences in IFN-gamma levels may not be detected in screening test [35], further analysis should be done to elucidate possible genetic defects [36]. Such primary immune deficiencies deserve special management thereafter. Other clues for primary immune deficiency, such as recurrent thrush, in a patient with axillary mycobacterial adenitis should raise clinical suspicion of a specific defect in IL-12/IFN-gamma axis [37].
Conclusion

Basically being a contagious disease, peripheral TLA is a relatively common entity in children. TLA differs from an ordinary suppurative lymphadenitis with a prolonged duration of inflammation process, lasting from weeks to months. The term scrofula, or scrofuloderma, is the classical nomination used to describe such a palpable TLA, spontaneously draining through a sinus formation. Sample collected from the lymph node in any method should be cultured for both tuberculosis and common pyogenic agents. Preferred standard medical therapy is mainly composed of three or four major antituberculous agents, lasting for six months, meanwhile related to isoniazid resistance of the population. Surgical intervention should be individualized depending on the location of the disease and the clinical evaluation. The advantages of early surgical treatment are rapid healing, low recurrence rate and reduced hospital stay, leaving a good cosmetic result. The diagnostic and therapeutic work-out needs to be addressed both by specialist in infectious diseases and surgeon as a teamwork for a better care.

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