

# Peripheral Tuberculous Lymphadenitis: Clinical Approach in Diagnosis and Management and Role of Surgery

Tuberculous lymphadenitis is among the most frequent presentations of extra pulmonary tuberculosis (TB). Peripheral tuberculous lymphadenitis (pTBL) is a common manifestation of extra-pulmonary TB, accounting for about 4.0–5.1% of all TB cases and 20.3–50.0% of extrapulmonary TB

Tuberculous lymphadenitis in the cervical region is known as scrofula<sup>1</sup>. Nontuberculous mycobacteria may also cause peripheral lymphadenitis, especially in those suffering from human immunodeficiency virus (HIV) co-infection. TB is responsible for up to 43 percent of peripheral lymphadenopathy in resource-limited settings<sup>2</sup>. In rural India, the prevalence of tuberculous lymphadenitis in children up to 14 years of age is approximately 4.4 cases per 1000<sup>3</sup>. In the United States, about 20 percent of patients with TB have extrapulmonary disease, and lymphadenitis is a presenting symptom in about 30 to 40 percent of cases<sup>4–6</sup>. In a Danish reported including more than 480 patients with TB between 2007 and 2016, lymphadenitis was observed in 13.5 percent of cases<sup>7</sup>.

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) 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<sup>8</sup>.

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”. In some patients, however, a preceding acute respiratory tract infection may augment this inflammation, transforming it to a modest tumor arousing pain (peri lymphadenitis)<sup>9</sup>. 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. The term scrofula, or scrofuloderma, is the classical nomination used to describe such a palpable TLA, spontaneously draining through a sinus formation. 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.

Definitive diagnosis of TLA is essential by means of microbiological confirmation either by molecular methods<sup>10</sup> or by culture, and also with histopathological workout compatible with characteristic cytomorphology<sup>11</sup>. 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<sup>12</sup>. 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. Biopsy obtained using FNA also enables a rapid diagnosis in pediatric mycobacterial lymphadenitis using nucleic acid

amplification such as the Xpert MTB/RIF test<sup>13</sup>. Surgical drainage of the suppurative abscess along with the remnants of the lymph node allows obtaining material both for microbiological and histological confirmation. Its timely diagnosis requires a high index of suspicion and histologic and microbiologic analyses due to its indolent clinical characteristics.

American Thoracic Society (ATS) guidelines recommend a 6-month course of therapy for pTBL that consists of a 2-month period of isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA) followed by INH and RIF for an additional 4 months. Although previous studies have demonstrated a high success rate in the treatment of pTBL with the 6-month regimen, many patients undergo a prolonged treatment course or suffer disease relapse.

There remains uncertainty regarding the treatment strategy for patients with peripheral tuberculous lymphadenitis (pTBL) in areas endemic for tuberculosis. To assess the predictors of a complicated treatment course in pTBL a retrospective analysis of 97 pTBL patients from January 1995 through to December 2004 was conducted in Taiwan. Patient characteristics with and without a complicated treatment course, defined as prolonged treatment (> 9 months) and/or relapse, were compared for determining the predictors. Results showed the disease occurred predominantly in females (57.7%) with a mean age of 37. Most patients (72%) were asymptomatic. Cervical nodes were the most common (72%) manifestations. Fifty-six patients completed a 6–9 month course of therapy without relapse; 28 had a prolonged but complete treatment course, and 13 relapsed within a mean of 8.5 months after treatment (range, 3–42 months; median, 7.8 months). Of 97 pTBL patients, six had enlarged or newly appeared lymph nodes during treatment. Multivariate analysis indicated that low body mass index and bilateral cervical nodes were independent determinants of a complicated treatment course with the odds ratios of 1.2 (95% CI, 1.01–1.41;  $p=0.042$ ) and 3.9 (95% CI, 1.08–14.0;  $p=0.038$ ), respectively. In conclusion this study found that pTBL is more likely to occur in young female patients. For patients who present with bilateral cervical nodes and low body mass index, a prolonged treatment course to ensure disease control should be considered<sup>14</sup>.

The absence of healing criteria increases the therapeutic difficulties observed despite a well controlled compliance in patients with tubercular lymphadenitis. One prospective study including patients treated for lymph node tuberculosis in the tuberculosis control departments of five departments in Algeria during the year 2017 for tuberculosis. Case treatment outcomes were assessed by comparing three groups according to the duration of treatment (6, 9 and 12 months). Results: Of the 4279 cases of tuberculosis recorded, 3327 patients were treated for extra-pulmonary tuberculosis (77.7%), including 2329 cases of lymph node tuberculosis. The sex ratio is 0.43. The personal and/or family history of tuberculosis was found in 27.4% of cases. A comorbidity including diabetes was found in 13% of cases. Cervical involvement predominates with 87.5% of cases. The association with pulmonary tuberculosis or other extra-pulmonary disease was recorded in 11%. Tuberculosis origin was proven in 67% and presumed in 33%. Healing was defined as complete disappearance or lymphadenopathy less than 15 mm. Among the 2329 patients, 1607 were declared cured at the end of the 6th month, 1647 after 9 months and 1653 cases after 12 months of treatment. The use of surgery was necessary in 11% of cases. From this study the multidisciplinary approach focused on the active participation of all specialists in ganglionic tuberculosis to improve therapeutic practices and lead to consensual behaviors<sup>15</sup>.

Tuberculosis-immune reconstitution inflammatory syndrome is an excessive immune response against *Mycobacterium tuberculosis* that may occur in either HIV-infected or uninfected patients, during or after completion of anti-TB therapy. In HIV-infected patients it occurs after initiation of antiretroviral therapy independently from an effective suppression of HIV viremia. There are two forms of IRIS: paradoxical or unmasking. Paradoxical IRIS is characterized by recurrent, new, or worsening symptoms of a treated case. Unmasking IRIS is an antiretroviral-associated inflammatory manifestation of a subclinical infection with a hastened presentation. The pathogenesis is incompletely understood and the epidemiology partially described. No specific tests can establish or rule out the diagnosis. Treatment is based on the use of anti-tuberculosis drugs sometime with adjunctive corticosteroids. Mortality is generally low<sup>16</sup>.

The therapeutic response of cervical tuberculous lymphadenitis (CTBL) may be delayed or paradoxical, with the frequent development of residual lymph nodes (LNs) during and after antituberculous treatment. A study investigating the incidence of residual LNs and the clinical, radiological, microbiological, and pathologic responses of patients with CTBL after 6 months of antituberculous therapy in Korea University Ansan Hospital medical records of HIV-negative adult patients with CTBL diagnosed between July 2009 and December 2017 were analyzed. After 6 months of first-line antituberculous treatment, computed tomography (CT) scans were conducted to evaluate for residual LNs. Fine-needle aspiration biopsy (FNAB) was carried out if a patient presented with residual LNs > 10 mm in diameter with central necrosis, peripheral rim enhancement, or perinodal inflammation on CT scan. Residual LNs were detected in 35 of 157 patients who underwent follow-up CT scans and were more commonly observed in younger patients who completed the treatment (mean years±standard deviation [SD]: 33 ± 13 vs. 44 ± 16,  $p < 0.001$ ). The recurrence rate was approximately 5%, which was not significantly different in both groups. Among the 15 patients who underwent FNAB, 3 (30%) presented with granuloma, and 2 of 15 and 10 of 14 patients had positive AFB and TB PCR results, respectively. The TB culture results of 15 patients were negative. Residual LNs may still be observed after 6 months of antituberculous treatment. Although the radiologic and pathologic findings after treatment are still indicative of TB, not all residual LNs indicate recurrence or treatment failure. A six-month therapy may be sufficient for cervical tuberculous lymphadenitis<sup>17</sup>.

There is considerable argument about the modality and timing of surgical management. 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. During the suppurative stage, whether presenting with spontaneous drainage or not, a simple incision and drainage 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. A second operative intervention and an excisional biopsy in the operating room is indicated, in case of failure in total extirpation [18]. 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. 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. 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<sup>19</sup>.

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<sup>20</sup>. Finally, FNA of the relevant node requires no sophisticated equipment to perform but a resultant draining sinus tract usually resistant to spontaneous healing, further forming unsightly cheloids will promote surgical removal.

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<sup>8</sup>. 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. 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<sup>21</sup>.

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<sup>22</sup>.

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**Prof. Md. Atiquel Islam Chowdhury**  
Professor, Department of Medicine  
Southern Medical College, Chittagong  
01715086192, mcatiuel04@gmail.com

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