

## Scrofula Revisited: An Update on the Diagnosis and Management of Tuberculosis of Superficial Lymphnodes

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**Abstract:** Lymphnode tuberculosis is a disease of great antiquity. It is the commonest form of extra-pulmonary tuberculosis, and is probably the commonest cause of chronic lymphadenitis in children. Even after the advent of effective chemotherapy for tuberculosis, it still poses considerable problems in diagnosis and management. The disease usually presents as a painless lymphadenopathy of the superficial lymphnodes of insidious onset, which may proceed to abscess and sinus formation if neglected. Cervical nodes are most commonly affected, but multiple node involvement is common. Differential diagnosis include other infections, neoplasia, congenital conditions in the head and neck and rarely, drug reactions. Diagnosis, whenever feasible, should be made on the basis of histological evidence after lymphnode biopsy. Diagnosis, made on clinical grounds has poor specificity and will result in a great degree of over diagnosis. Recently, the role of fine needle aspiration cytology as an initial screening procedure has been recognized. The Tuberculosis Research Centre carried out the first clinical trial which established the efficacy of short course chemotherapy in the treatment of childhood lymphnode tuberculosis. In 168 children with biopsy confirmed lymphnode tuberculosis treated with an intermittent six month regimen, the cure rate after five years was 95%. The Revised National Tuberculosis Control Programme recommends that patients with lymphnode tuberculosis (Category 3) should be treated with rifampicin and isoniazid three times a week for six months, with pyrazinamide for the first two months.

**Key words:** *Tuberculous Lymphadenitis; Scrofula; Chemotherapy.*

Tuberculosis of the superficial lymphnodes is the commonest extra-pulmonary manifestation of the disease. In India, approximately 10-15% of all tuberculosis cases are extra-pulmonary, and of these 2/3<sup>rd</sup> are due to lymphnode disease<sup>1</sup>. Known as scrofula, the disease figures prominently in the writings of Hippocrates (460-377 BC) and Herodotus (484?-425?BC). During the Middle Ages it was widely prevalent throughout Europe, and was known as the King's Evil, and was believed to be cured by the Royal Touch<sup>2</sup>. However, it was not until the 19<sup>th</sup> century, with the emergence of pathology as a science, that the tuberculous etiology of scrofula was recognized.

The advent of the HIV pandemic has had an adverse impact on the global epidemiology of tuberculosis. It has been one of the major causes for the resurgence of tuberculosis in the developed nations and has aggravated the already grim tuberculosis situation in many countries in Africa and Asia<sup>3</sup>. This association seems to be particularly well marked for extra-pulmonary tuberculosis, especially lymphadenitis which makes the diagnosis and management of this disorder more complicated. Studies in Africa have suggested that HIV positivity of tuberculous lymphadenitis patients

decreased the possibility of histology and culture, both being indicative of tuberculosis<sup>4</sup>. Co-infection with HIV influences several clinical and laboratory features in patients with tuberculous lymphadenitis<sup>5</sup>.

### CLINICAL FEATURES

Historically, scrofula has been a common disease in children. However, in western countries, in the recent past, numerous studies have shown a peak age range of 20-40 years. This shift in age probably reflects the falling incidence of childhood tuberculosis in the developed countries<sup>6</sup>. In India the disease is still common in children and in young adults<sup>7,8,9,10</sup>. In a large clinical trial on lymphnode tuberculosis conducted by the Tuberculosis Research Centre (TRC) in Madurai, South India (*manuscript in preparation*), 35% of patients were aged 12 years or less and 87% were aged 30 years or below. More than 50% of patients were in the 13-30 years age group.

While pulmonary tuberculosis is more common in males, tuberculous lymphadenitis in adults shows a striking female preponderance<sup>6,9,10,11</sup>. In the TRC clinical trial in Madurai, there was a strong female to male excess in the 13-30 year age group. However, in children, this female preponderance is not seen<sup>9,10</sup>. There was a slight excess of males in the Madurai study, and in an earlier clinical trial conducted by the TRC on childhood lymphnode tuberculosis in Chennai, there were equal

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number of males and females<sup>12</sup>. The reasons for this discrepancy are not clear. Perhaps hormonal changes associated with puberty and child bearing have a role to play.

Tuberculous lymphadenitis usually presents as a slowly progressive painless enlargement of the lymphnodes of the neck and sometimes of the axilla or groin. Untreated, the disease may progress to abscess and sinus formation. The physical appearance of superficial tuberculous lymphadenitis has been classified into five stages by Jones and Campbell<sup>13</sup>. Stage 1-enlarged, firm, mobile, discrete nodes; Stage 2-large, rubbery nodes fixed to surrounding tissues owing to periadenitis; Stage 3-central softening due to abscess formation; Stage 4-collar stud abscess formation; and Stage 5-sinus tract formation.

The cervical lymphnodes are the most commonly affected group in tuberculosis. In order of decreasing frequency, the anterior and posterior cervical, the supravclavicular and the submandibular nodes are involved. This was true in both the TRC clinical trials in Chennai and Madurai. More than 80% of the children had cervical node involvement. Noteworthy was the frequency with which multiple groups of nodes were affected. In the Chennai study, 32% of the children had four groups of nodes affected and 10% had five or six groups affected. Isolated axillary node involvement was seen in 6% and isolated inguinal node involvement in 8% of patients. Atypical node involvement were also seen: femoral, pectoral, epitrochlear.

### DIAGNOSIS

The diagnosis of tuberculous lymphadenitis has always posed a challenge to the clinician.

The differential diagnosis of this condition are many:

1. Neoplasia - Hodgkin's and Non-Hodgkin's lymphoma, sarcoma.
2. Other infections-acute bacterial infections, viral infections (infectious mononucleosis), chlamydia, toxoplasmosis, fungal infections, non-tuberculous mycobacterial infections, BCG adenitis.
3. Drug reactions - e.g. hydantoin.
4. Sarcoidosis.
5. Non lymphnode swellings - submandibular or parotid glands, branchial cyst, cystic hygroma, carotid body tumor, thyroid swellings.

The diagnosis is often made on clinical grounds. Biopsy of the node is not always done. This may be due to the fact that either facilities are not available, especially in rural areas, or reluctance on the part of the patients to undergo the biopsy. The importance of lymphnode biopsy in the diagnosis of this disorder is well illustrated in the

TRC clinical trials. In the Chennai study, laboratory confirmation of the diagnosis was obtained in less than 50% of the children in whom the pediatrician made a clinical diagnosis of tuberculous lymphadenitis. Of 373 biopsies done on children in Madurai, histological evidence to support the clinical diagnosis was available in only 126(34%). Thus it is clear that the specificity of clinical diagnosis is low, and a biopsy must be done whenever feasible. Serial sections should be examined. If diagnosis is made only on clinical grounds a large number of patients would receive unnecessary treatment. This is not a new finding and has been highlighted by Pamra and Mathur in their classic study on tuberculous lymphadenitis in 1974. Of the 44 children <10 years of age out of a total of 285 cases of cervical lymphadenitis from eight centers, only 25 (57%) were confirmed as tuberculosis, 18 (41%) as non-specific lymphadenitis and 1 (2%) as malignancy<sup>9</sup>. Fourteen years later the scenario was no different, with only 23 of 62 (37%) children with cervical lymphadenitis being confirmed as tuberculosis<sup>10</sup>.

Four distinct types of histological features were seen in lymphnode biopsies in children at TRC<sup>14</sup>. Most common was the 'reactive' type with typical tuberculous granuloma, with fine eosinophilic caseation necrosis, epithelioid cells, giant cells, plasma cells and lymphocytes, constituting 54% of all cases. Next in frequency was the 'hyperplastic' type with well differentiated epithelioid cell granuloma with very little necrosis (29%). The remaining were 'hyporeactive' type-a poorly organized granuloma with macrophages, immature epithelioid cells, lymphocytes, plasma cells and coarse predominantly basophilic caseation necrosis (12%) and a 'non-reactive' type - unorganized granuloma with macrophages, lymphocytes, plasma cells and polymorphs with non caseating necrosis (5%).

The importance of naked eye examination of nodes should not be underestimated in the diagnosis, pending confirmation by histology. In a Zambian study, 148 (79%) of 188 cases of tuberculous lymphadenitis showed non-caseating tuberculomata or caseation visible on naked eye examination of the biopsied lymphnode<sup>15</sup>. Some workers have described the usefulness of impression smears from the cut surface of the lymphnode.

### Fine Needle Aspiration Cytology

Recently there have been a number of reports on the value of Fine Needle Aspiration Cytology (FNAC), in the diagnosis of tuberculous lymphadenitis with claims of sensitivity and specificity of 80-90% and diagnostic accuracy above 80%. This outpatient procedure has provided an alternative and easy method for collection of material for cytomorphologic and bacteriologic

examination. Diagnosis of tuberculosis can be made by the demonstration of epithelioid granulomas with or without caseation even in the absence of acid fast bacilli (AFB). Necrotic features whether a cellular or accompanied by neutrophilic infiltrate are usually misdiagnosed as suppurative abscesses. Such smears however, show AFB positivity and thus the diagnosis of tuberculosis is still possible even in the absence of epithelioid granulomas. Therefore, it has been suggested that all smears of suspected tuberculous lesions obtained by FNAC should be subjected to Ziehl-Neelson (ZN) staining for AFB<sup>16</sup>.

A study from Bombay has shown another interesting diagnostic feature. FNAC smears sometimes reveal multiple pink, homogenous structures with irregular shape and well defined margins called 'eosinophilic structures'. Immunoperoxidase staining demonstrated these 'eosinophilic structures' to be degenerated granuloma and thus form an extended diagnostic criterion<sup>17</sup>.

FNAC is of particular use in patients presenting with multiple nodes, a common enough clinical presentation in our setting. In a patient with multiple lymphadenopathy, deciding on which node to biopsy can be difficult because some of the enlarged nodes may not reflect the true disease process. When such a lymph node is biopsied, the actual diagnosis can be delayed or even missed. FNAC is advantageous in such situations. Many, if not all, of the enlarged lymph nodes can be sampled at one sitting. If this procedure fails to provide a definitive diagnosis, the clinician should then proceed to do an open biopsy<sup>18</sup>.

However, the detection rate for *Mycobacterium tuberculosis* from the aspirated material is usually low with ZN stain and even with culture. The application of the polymerase chain reaction (PCR) for mycobacterial DNA to the aspirated material yields excellent results. PCR is the most sensitive technique in the demonstration of tuberculosis in patients with clinically suspected tuberculosis of the lymph nodes, who have AFB stain or culture negative cytology<sup>19</sup>.

FNAC can also be performed under ultrasound guidance for deep seated nodes. It may be necessary to perform several aspirations from different sites of the enlarged lymph node. Thus FNAC is a valuable addition to the diagnostic armamentarium. A diagnosis of 'granulomatous lymphadenitis consistent with tuberculosis' can be given even if acid-fast stains are negative. An open biopsy should be recommended if there is a discrepancy with the clinical impression.

### Bacteriology

Lymphnode tuberculosis, like other forms of extra-

pulmonary disease is a pauci bacillary condition. Therefore, it is not surprising that in many studies on lymphnode tuberculosis, the yield of positive cultures from the lymphnodes have not been high. However, using appropriate techniques, it is possible to culture *Mycobacterium tuberculosis* in a majority of the cases. At the TRC, multiple media like LJ medium, LJ with pyruvate, 7OH11 oleic acid medium and liquid Kirchner's medium are used for culturing *Mycobacterium tuberculosis* from extra pulmonary specimens including lymphnodes<sup>20</sup>. Using a transport medium (liquid Kirchner's medium) when there is a likely delay in sending the specimen to the laboratory also contributes greatly to increased culture positivity<sup>21</sup>. With these multiple culture media, the culture positivity for lymphnode specimens was 62% in the TRC Chennai study<sup>12</sup> and 74% in the Madurai study. These are high figures for extra-pulmonary specimens and was possible only with the use of multiple culture media. Discharges from sinuses should also be cultured for mycobacteria. However, the use of multiple culture media is feasible only in a research setting.

In western countries mycobacterial lymphadenitis in children, except in the Asian immigrant community, is caused almost exclusively by non-tuberculous mycobacteria<sup>22,23</sup>. In India the causative agent is invariably *M.tuberculosis*. Histologically, it is difficult to distinguish lymphadenitis caused by *M.tuberculosis* from that caused by non-tuberculous mycobacteria, though some authors have described certain minor differentiating features<sup>24</sup>.

### Tuberculin Test

The cutaneous reaction to PPD is often used as an aid to the clinical diagnosis of tuberculous lymphadenitis in practice. Pamra and Mathur found that in 22 children below 15 years, with confirmed tuberculous lymphadenitis, only one had an induration below 5 mm, whereas of 20 children in the same age group with lymphadenitis of other causes, 11 had a reaction of less than 5 mm. If an induration of 10mm or more is taken as evidence of positivity, then five of the 22 children would be labeled as negative. The authors, therefore, suggested that an induration 5mm to 1 TU PPD RT 23 should be considered as evidence of infection<sup>9</sup>. In the TRC Chennai clinical trial, 154 of 168 (92%) children had an induration of 10mm or more to 1 TU PPD RT 23. Only 14 (8%) children had a negative reaction. What was interesting was the large number of patients with large reactions: one hundred and forty seven (88%) children had an induration of 15 mm or more and 107 (64%) had induration of 20 mm or more<sup>12</sup>. This tendency for large reactions was also observed in the TRC Madurai study.

## Radiology

Seventy one percent of the children with tuberculous lymphadenitis in the TRC Chennai clinical trial had normal chest X-rays<sup>12</sup>.

With the recent rapid advances in the science of imaging technology, these techniques have also been used in superficial lymphadenitis. Studies have been published on the value of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in lymphadenitis of various causes<sup>25</sup>. While these sophisticated and expensive techniques have a definite role in the diagnosis of intra thoracic lymphadenopathy, their necessity in superficial lymphadenitis is questionable. The diagnostic features on CT scan of tuberculous lymphadenitis are central low density and peripheral rim enhancement that tends to be thick and irregular compared with a malignant lymphadenopathy<sup>26</sup>.

## MANAGEMENT

While the treatment of pulmonary tuberculosis has been systematically studied over the years by a number of randomized clinical trials in India and elsewhere, the same is not true for lymph node tuberculosis. There has never been any consensus on the management of this disorder. Practices adopted in the past have included complete surgical excision of the node masses, anti - TB chemotherapy of various duration and a combination of the two<sup>27</sup>.

The British Thoracic Society Research Committee first attempted to systematically study the medical treatment of tuberculous lymphadenitis. In a series of three well designed prospective randomized clinical trials between 1977 and 1993 the duration of treatment for this disorder was reduced progressively from 18 months to 9 months to 6 months<sup>11,28,29,30</sup>. However, these studies were in adult patients. There is paucity of information on the treatment for tuberculous lymphadenitis in children. The TRC, Chennai carried out the first collaborative clinical trial on the efficacy of short course chemotherapy for childhood tuberculous lymphadenitis<sup>12</sup>. In this study 168 children 1- 12 years of age with biopsy confirmed tuberculous superficial lymphadenitis, were treated with a fully supervised six month regimen consisting of isoniazid, streptomycin, rifampicin and pyrazinamide thrice a week for two months followed by isoniazid and streptomycin twice a week for four months (2SHRZ<sub>3</sub>/4SH<sub>2</sub>). The study in which patients were followed up for five years showed that the regimen was highly successful with a 95% cure rate. The response to treatment in the children, a majority of whom had extensive and severe lymphadenitis was very rapid. In patients presenting with sinuses and abscesses, 81% of the lesions had healed by

one month of treatment, 95% by three months and all by the end of treatment. The regimen was well tolerated with few patients experiencing side effects.

Meanwhile, evidence emerged that extrapulmonary tuberculosis, being a paucibacillary condition could be effectively managed with a less potent regimen. So the TRC initiated the second clinical trial in Madurai, South India, in which two six month regimens using only rifampicin and isoniazid, with or without pyrazinamide were compared for the treatment of tuberculous lymphadenitis. The results will be published shortly.

A number of clinical trials have now shown the efficacy of a six month short course regimen for the treatment for superficial tuberculous lymphadenitis. It is now well established that surgery has a limited role in the management of this disease. In review of the management of 85 children with tuberculous lymphadenitis, surgery consisted only of procedures such as a diagnostic biopsy or rebiopsy, FNAC, drainage of abscesses and excision of sinuses<sup>31</sup>. At TRC there was never an occasion to resort to excision of nodes at any stage in the two clinical trials.

A matter of practical importance in the management of tuberculous lymphadenitis is the occurrence of enlargement of nodes or the appearance of new nodes after treatment is initiated. Fresh abscesses sometimes appear or existing abscesses break down. These events usually subside spontaneously when treatment is continued without modification or change of the regimen. These events are also observed after treatment is completed and when patients are followed up. In the TRC Chennai clinical trial 32 patients had 36 episodes of enlargement or fresh appearance of nodes and fresh abscesses and sinuses appeared in four and six patients respectively<sup>12</sup>. These paradoxical responses have been reported by many authors and probably represent an immune response to the release of mycobacterial products caused by the bactericidal activity of the regimens<sup>11,28,29,30</sup>. This observation is of great practical importance as the appearance of new nodes or the enlargement of nodes while on treatment is often a cause of alarm to the patient and of concern to the treating physician. However, this development is not always an indication that treatment has failed and often does not warrant a change of the treatment regimen.

It is also important to realize that the nodes do not always disappear completely at the end of treatment. Thirty percent of patients in the TRC Chennai study had residual small nodes palpable (<10mm diameter) at the end of successful chemotherapy<sup>12</sup>. Repeat biopsy showed that in most of these cases the histology was not suggestive of tuberculosis and the culture for mycobacteria was

negative.

The Revised National Tuberculosis Control Programme (RNTCP), being implemented in a phased manner all over the country categorizes tuberculosis patients into three groups for purposes of treatment, based on site and severity of disease, and whether the patient had received any treatment for tuberculosis in the past<sup>33</sup>. Extra pulmonary tuberculosis, other than severe forms (such as meningitis, gastro-intestinal, renal, pericardial, spinal and disseminated TB) is classified as category III and the regimen recommended is two months of rifampicin, isoniazid, and pyrazinamide followed by four months of rifampicin and isoniazid, three times a week throughout (2RHZ<sub>3</sub>/4RH<sub>3</sub>). Numerous clinical trials in India and elsewhere have proved the efficacy of intermittent treatment for tuberculosis. Intermittent regimens, where the drugs are administered twice or thrice a week rather than daily, are as effective as daily regimens while proving less expensive and less toxic. They also permit the direct supervision of treatment, the cornerstone of the DOTS strategy of the RNTCP. Thus, lymphnode tuberculosis without pulmonary involvement in children can be successfully treated with this regimen.

The dosage recommended is as follows: the thrice weekly dosage is used in the RNTCP.

	Daily (mgm/kg)	Thrice weekly (mgm/kg)
Isoniazid	5	10
Rifampicin	10	10
Pyrazinamide	25	35
Streptomycin	15	15

### SUMMARY

1. Superficial lymphnode tuberculosis is the commonest form of extra pulmonary tuberculosis constituting about 7 - 10% of all cases. It is predominantly a disease of children and young adults in our country.
2. Cervical nodes are most commonly affected. Multiple node involvement is common, particularly in children.
3. The causative agent is almost always *Mycobacterium tuberculosis* in India.
4. Clinical diagnosis, especially in children has poor specificity. Biopsy should be done whenever possible. FNAC should be used as a screening procedure.
5. Treatment with short course chemotherapy is very effective. The regimen recommended is two months of rifampicin, isoniazid and pyrazinamide followed by four months of rifampicin and isoniazid, three

times a week throughout.

6. The role of surgery is usually reserved for diagnostic biopsy and draining of abscesses, if necessary.
7. Lymphnodes may enlarge or new nodes may appear during treatment. In most instances this does not warrant a change of treatment.

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