

Original Article

ANALYSIS OF TREATMENT OUTCOME OF SUPERFICIAL TUBERCULOUS LYMPHADENITIS ON THE BASIS OF CYTOMORPHOLOGICAL FEATURES

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Dutt NC, Gupta AM. Analysis of Treatment Outcome of Superficial Tuberculous Lymphadenitis On The Basis of Cytomorphological Features. Natl J Community Med 2014; 5(4);474-9.

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ABSTRACT

Introduction: Cases of tuberculous lymphadenitis continue to present clinical hurdles in successful treatment outcome. This study was aimed to analyze the cytomorphological features in superficial tuberculous lymphadenitis and to analyze the treatment outcome on the basis of these features.**Methods:** The present study was carried out in 60 patients of superficial palpable lymph nodes. All cases were subjected to fine needle aspiration of the lymph nodes.**Results:** Majority of patients were female and below 30 years of age. Cervical lymph nodes were most commonly involved 42(70%). It was seen that 48(80%), the lymph nodes had completely resolved. 9 were considered as failures. Cases were divided into 4 groups depending on cytopathological features i.e. group I- Abscess (15), group II- Caseous necrosis(16), group III-Epitheloid granuloma with caseation(17) and group IV Epitheloid granuloma without caseation(12) one patient from group I and one patient from group III defaulted. On follow-up with AKT group IV patients responded best. Cases with group IV cytopathological features had no failures (100% cure) while group I, group II, group III had 70%, 72% and 92.3% success rate respectively. Among the necrotizing lesion the best prognosis was seen in granuloma without caseation.**Conclusion:** Tuberculous lymphadenitis is more common in females with cervical lymph nodes most commonly involved. Presence of necrosis in lesions had greater chances of non-regression and failures.**Key words:** Tuberculosis, tuberculous lymphadenitis, outcome, treatment failure

INTRODUCTION

Lymph nodes are the easily accessible components of lymphoid tissue that not only clean and filter lymph but also produce lymphocytes and antibodies. The human body has approximately 600 lymph nodes, some of which (submandibular, axillary or inguinal lymph nodes) may normally be palpable in healthy people. Lymphadenopathy refers to nodes that are abnormal in size, consistency or number. It is one of the commonest and significant clinical presentations

of patients, attending the outdoor clinics in most hospitals.¹

The definition of EPTB disease under the RNTCP follows the international classification². EPTB is defined as TB of organs other than the lungs, such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, tubercular meningitis, tuberculoma of the brain, etc. Lymph node tuberculosis constitutes 20-40% of extrapulmonary tuberculosis. It is more common in children and women than other forms of extrapulmonary

tuberculosis and is more common in Asians and Pacific islanders. In developing and under developed countries, it continues to be caused by *Mycobacterium tuberculosis* and atypical mycobacteria are seldomly isolated. Commonly involved superficial lymph nodes (Scrofula or king's evil) include those in posterior and anterior cervical chains or the suprascapular fossae but others like submandibular, periauricular, inguinal and axillary groups may also be involved. Often, the lymphadenopathy is bilateral and noncontiguous. Intrathoracic (hilar, paratracheal and mediastinal in decreasing order) and abdominal lymph nodes are also involved in tuberculosis. Frequency of associated pulmonary involvement varies from 5% to 62% Management of lymph node tuberculosis often presents difficulties.

HIV co-infection has considerably changed the epidemiology of tuberculosis. Tuberculous lymphadenitis is the more common form of extrapulmonary tuberculosis in these patients. Further, it is more common than lymphoma, Kaposi's sarcoma and generalised lymphadenopathy of HIV. These patients are often older and males, involvement of multiple sites is more common and the anterior and posterior mediastinal group of lymph nodes are more often involved. A virulent form of disseminated disease may be seen in patients with AIDS. Tender lymphadenopathy, fever, weight loss and co-existing pulmonary tuberculosis are more common in HIV seropositive patients as compared to HIVseronegatives.³

OBJECTIVES

Objective is to study the cytomorphological features in superficial tuberculous lymphadenitis and the treatment outcome on basis of these features.

METHODS

Lymph Node TB (LNTB) is the commonest form of EPTB. LNTB is considered to be the local manifestation of a systemic disease. Patients usually present with slowly enlarging lymph nodes and may otherwise be asymptomatic. In HIV-negative patients, isolated cervical lymphadenopathy is most often seen in about two-thirds of the patients. In HIV-positive patients, multifocal involvement, intra-thoracic and intra-abdominal lymphadenopathy and associated pulmonary disease are more common. Physical examination

may be unremarkable but for palpable lymphadenopathy. Occasionally, a lymph node abscess may burst leading

to a chronic non-healing TB sinus and ulcer formation The present study was carried out in the Pulmonary Medicine Department, Smt.N.H.L Municipal Medical College, Ahmadabad from March 2013 to July 2014 who presented with superficial palpable lymphnodes .

Aspiration was done using a 20-23 gauge needle and disposable 10 ml plastic syringe. In all cases, alcohol fixed and air-dried smears were made: alcohol fixed slides were stained H&E method. Special stain for acid fast bacilli (Z-N stain) was done in all cases where purulent or cheesy material was aspirated and smears showed granulomatous lymphadenitis. All the stained smears were evaluated by a pathologist and a diagnosis given based on cytomorphological features. On the basis of cytomorphology, patients were divided into the following groups. Group 1 Abscess Group 2 Caseous necrosis Group 3 Epitheloid granulomas with caseation Group 4 Epitheloid granulomas without caseation. The data entry was carried out using Microsoft Office Excel worksheet and analyzed.

RESULT

Majority of patients were female and below 30 years of age. Cervical lymphnodes were most commonly involved 42 (70%). No organisms could be isolated on LJ media in case of non-necrotizing lesions. Two patients defaulted from study. At end of treatment, it was seen that 48(80%), the lymphnodes had completely resolved. 9 were considered as failures. Cases were divided into 4 groups depending on cytopathological features i.e. group I- Abscess (15), group II- Caseous necrosis (16), group III-Epitheloid granuloma with caseation (17) and group IV Epitheloid granuloma without caseation (12) one patient from group I and one patient from group III defaulted. On follow-up with AKT group IV patients responded best as no new lymphnode appeared, while in rest of three groups new lymphnodes appeared (one in each group). Cases with group IV cytopathological features had no failures (100% cure) while group I, group II, group III had 70%, 72% and 92.3% success rate respectively. None had discharging or ulcer formation. Among the necrotizing lesion the best prognosis was seen in granuloma without caseation.

Table 1. Distribution of Cases of Lymphadenopathy by Age, Sex and Site

Sex Age in years	Male			Total	Female			Total
	<18	18-40	>40		<18	18-40	>40	
Site								
Cervical	3	8	4	15	3	21	3	27
Supraclavicular	1	1	2	4	1	3	1	5
Axillary		1	1	2	1	1	1	3
Inguinal		1	1	2	1	1		2
Total	4	11	8	23	4	29	4	37

Table 2. Incidence of various types of cytologic picture with Treatment Outcome

Group	Cytological features on Aspirated smear	Cases (%)	Outcome (%)
I	Abscess formation	15 (25.0)	70
II	Caseous necrosis	16 (26.6)	72
III	Epitheloid granuloma with caseation	17 (28.3)	92.3
IV	Epitheloid granuloma without caseation	12 (20.0)	100

DISCUSSION

Tuberculous lymphadenitis usually presents as a slowly progressive, painless swelling of a single group of lymph nodes⁸. The duration of symptoms at the time of presentation is typically 1-2 months, varying from 3 weeks to 8 months^{4, 8}. In a series of patients in India, the mean duration of symptoms was significantly longer in men than in women⁸. Median lymph node size is 3 cm, but nodes may be up to 8-10cm in diameter⁶. Patients do not generally report significant pain at presentation, and node tenderness during examination is noted in only 10%-35% of cases^{6, 7}. A draining sinus may be present in 4%-11% of cases^{7, 8}. Unilateral involvement of 1-3 nodes has been noted in 85% of cases⁸. Cervical chain involvement is most common and is reported in 45%-70% of cases, with 12%-26% in the supraclavicular region; 20% of cases are bilateral^{4, 6, 7}. In a study from Zambia, symmetrical adenopathy with nodes typically, 3 cm was reported in 94% of patients with HIV-induced lymphadenopathy, compared with 29% of patients with HIV-associated tuberculous lymphadenitis. In contrast, symmetrical adenopathy was observed in only 11% of HIV-negative patients with tuberculosis lymphadenitis, and nodes in this group were typically, 3 cm. Rates of systemic symptoms reported in different series vary depending in part on geographic origin and case selection. In a series of 104 predominantly HIV-negative patients from California, fever was reported in 19% and weight loss in 16%⁴. In contrast, fever and weight loss were reported in 40%-60% of HIV-negative patients in series from Qatar and India⁷.

⁸. Systemic symptoms are reported more frequently in HIV-positive patients than in HIV-negative patients (76% of 21 vs. 12% of 43 in a report from Taiwan) [6]. Concomitant pulmonary tuberculosis is reported in 18%-42% of patients with higher rates among HIV-positive patients than among HIV-negative patients (90% of 10 vs 28% of 25 in a study from Los Angeles). HIV-positive patients with tuberculous lymphadenitis typically have a higher rate of disseminated disease than do HIV-negative patients (38% vs 8%; P, <.001).

The major pitfalls in the diagnosis of EPTB are atypical clinical presentations simulating Other inflammatory and neoplastic conditions, resulting in delay or deprivation of treatment. Therefore a high index of suspicion is necessary to make an early diagnosis. In developing countries, the lack of diagnostic resources adds to the problems. This Often leads to empirical treatment based on clinical grounds without pathological and/or Bacteriological confirmation, leading to over-diagnosis and unnecessary treatment. This was shown in a study at TRC, Chennai, where only 34 percent of 373 biopsies done on Clinically diagnosed cases of LNTB had histopathological confirmation¹⁰. In clinical practice, the cutaneous reaction to PPD is used as an aid to the diagnosis. Its value as a diagnostic tool is limited in adults in India, since about 40 percent of the adult population is infected with TB⁹. However, it may be of use in children aged five years or below. The selection of the diagnostic procedures depends on the organ of involvement in EPTB. Fine needle aspiration of lymph nodes and cytological examination plus AFB smear and culture examination, appears to be the diagnostic procedure of choice in superficial TB lymphadenitis¹¹.

Tuberculous lymphadenitis needs to be differentiated from lymphadenopathy due to other causes. These include reactive hyperplasia, lymphoma, sarcoidosis, secondary carcinoma, generalized lymphadenopathy of HIV, Kaposi sarcoma,

lymphadenitis caused by Mycobacteria other than tuberculosis (MOTT), fungi, and toxoplasmosis. In general, multiplicity, matting and caseation are features of tuberculous lymphadenitis but these are neither specific nor sensitive. In lymphoma, the nodes are rubbery in consistency and are seldomly matted. In lymphadenopathy due to secondary carcinoma, the nodes are usually hard and fixed to the underlying structures or the overlying skin.

Firm diagnosis of tuberculous lymphadenitis requires demonstration of mycobacteria but the latter may not be found in several specimens that are ultimately proved to be tuberculous in aetiology. Further, obtaining a proper specimen may not always be easy. History of exposure to a person suffering from pulmonary tuberculosis is highly suggestive of lymphatic tuberculosis in a given clinical setting. Tuberculin skin test is positive in majority of patients of tuberculous lymphadenitis, the probability of false negative test is less than 10%. Thus a positive skin test seems to support the diagnosis and a negative test substantially reduces the likelihood of tuberculous lymphadenitis. Chest x-ray should be obtained in all the patients suspected to be suffering from tuberculous lymphadenitis. It not only excludes any co-existing intrathoracic disease but the presence of an active or healed pulmonary lesion acts as a supportive evidence for tuberculous lymphadenitis in cases where the diagnosis remains in doubt i.e. a compatible biopsy but a negative culture. Ultrasound examination of abdomen and CT scan of the chest may be required in some patients. Enlarged lymph nodes may show hypodense areas with rim enhancement or calcification. It may also demonstrate the status of the adjoining structures. It may also help obtaining pathological specimens for cyto-histopathology and culture. Traditionally, excision biopsy is done to diagnose tuberculous lymphadenitis but fine needle aspiration cytology (FNAC), a relatively less invasive, painless and outdoor procedure, seems to have established itself as a safe, cheap and reliable procedure. Typically, tuberculous lymph nodes show epithelioid cell granulomas, multinucleated giant cells and caseation necrosis. Caseating granulomas are seen in nearly all the biopsy specimens and 77% of the FNAC's. Alternative diagnostic methods such as polymerase chain reaction tests of the tissue to identify tubercle bacilli look promising but serological tests lack sufficient sensitivity or specificity to be of real utility. FNA has emerged as a first-line diagnostic technique, especially in tu-

berculosis-endemic countries, where the test is both sensitive and specific¹³. FNA is safer, less invasive, and more practical than biopsy, especially in resource-limited settings.

However, of note, in the majority of FNA studies from these regions, the diagnosis of tuberculosis was based on detection of granulomatous inflammation (GI). In settings where tuberculosis is not endemic, the finding of GI may not be as specific for tuberculosis. In a study of 97 cases from the United Kingdom 90% of which were in foreign-born patients, 67% of FNA specimens had positive culture results, and 79% had GI. Fifty-four (70%) of 77 FNA specimens with GI had cultures positive for *M. tuberculosis*¹³. In a study from California, 18% of FNA specimens from 180 patients (106 HIV-positive) yielded positive culture results. When positive culture results were combined with detection of AFB, the sensitivity of FNA specimens was 46% and specificity was 100%¹⁴. Among 106 predominantly HIV-negative cases from California, the rate of culture positivity from excisional biopsy and FNA specimens was similar (71% and 62% respectively; 4. Fluorescence microscopy using light-emitting diodes is an inexpensive and robust method of AFB smear analysis of FNA specimens from children with tuberculous lymphadenitis in South Africa¹⁷. Nucleic acid amplification tests (NAATs) may provide a rapid, specific, and sensitive means of diagnosis. In a study from India, 17 (77%) of 22 cases diagnosed by culture and detection of GI were detected by testing of excisional biopsy (82%) of 22 cases were detected⁶. A systematic review of NAAT in tuberculous lymphadenitis revealed highly variable and inconsistent results sensitivity, 2%–100%; specificity, 28%–100%, with more favorable performance from commercial assays and with sample sizes .20 uL [18]. In a study from Germany, 6 of 10 tuberculous lymphadenitis cases confirmed by culture were detected by the newer GeneXpert test; 3 cases with positive results had negative culture results, but subsequent investigation suggested that these were true cases¹⁹. samples, compared with 9 (41%) of 22 by testing of FNA samples. With the addition of NAAT of the FNA specimens, 18 Invasive procedures like mediastinoscopy, video assisted thoracoscopy or tranbronchial approach may become essential in a few patients with intrathoracic disease.

The Infectious Disease Society of America (IDSA) recommends 6 months of the following treatment for lymphadenitis caused by drug-susceptible organisms²⁰ isoniazid, rifampin, py-

razinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for another 4 months. The 6-month recommendation is supported by studies that showed no difference between 6 and 9 months of treatment in cure rates (89%–94%) or relapse rates (3%). The benefit of routine corticosteroid therapy for peripheral tuberculous lymphadenitis is unknown. A double blind, placebo controlled trial involving 117 children with lymph node endobronchial tuberculosis revealed a significantly greater improvement in those who received a 37-day tapering course of steroids. Only uncontrolled studies are available on treatment outcomes in adults with peripheral lymphadenitis^{21, 22}. Steroids have been used selectively for local discomfort²³, a significant issue for some patients in our experience. IDSA guidelines do not recommend the use of steroids in the treatment of tuberculous lymphadenitis²⁰. Adjuvant immunotherapy with anti-tumor necrosis factor agents has been studied in small numbers of patients for routine treatment of all forms of tuberculosis, but available data are insufficient to make a recommendation²⁴. IDSA guidelines recommend surgical excision only in unusual circumstances, and these circumstances are not defined explicitly²⁰. Although surgical excision combined with antibiotic therapy has produced favorable outcomes, we are not aware of controlled studies that have compared excision plus antibiotic therapy with antibiotic therapy alone. Two considerations suggest that early excisional biopsy be considered more frequently as an adjunct to antibiotic therapy, especially for patients at risk of PUR (e.g., those with baseline tenderness) in settings where expert surgical care is available and when cosmetic considerations are not a contraindication. First, some patients who respond to medical treatment have significant baseline and persistent nodal discomfort, which might be ameliorated by excision. Second, paradoxical upgrade reactions are common and uncomfortable and require additional medical visits and consideration of prolonged antibiotic therapy and/or corticosteroids, all of which might potentially be avoided by excision. Surgical excision should also be considered as an adjunct to antibiotic therapy for disease cause by drug resistant organisms. Surgical excision has been recommended for PUR and for treatment failure in cases of tuberculous lymphadenitis and for patients who have discomfort from tense, fluctuant lymph nodes^{4, 25}. In a retrospective review, aspiration, incision, and drainage or excision were associated with a trend toward a shorter duration of

PUR²². Surgical excision is the recommended therapy for cervical lymphadenitis due to nontuberculous mycobacteria in children and has been associated with better outcomes than 3 months of 2-drug antibiotic therapy²⁶⁻²⁸. A unique and disturbing feature of successful treatment of drug susceptible tuberculous lymphadenitis is the frequency with which patients experience worsening of symptoms during treatment (i.e., paradoxical upgrading reaction [PUR]). Reported rates of PUR vary and depend, in part, on the definition that has been applied. One definition is the development of enlarging nodes, new nodes, or a new draining sinus in patients who have received at least 10 days of treatment²². A narrower definition excludes earlier cases because it requires initial clinical improvement before worsening and does not include draining sinuses.⁵²

CONCLUSION

Tuberculous lymphadenitis is more common in females with cervical lymph nodes most commonly involved. Presence of necrosis in lesions had greater chances of non-regression and failures. Disease rates are highest among patients aged 30–40 years, and disease is more common among women and patients of Asian descent. Tuberculous lymphadenitis may respond slowly to standard antibiotic treatment, with persistent discomfort and the development of culture-negative paradoxical upgrading reactions in as many as 20% of patients. Frequent patient follow-up during treatment is recommended for reassurance and management of local discomfort. Initial surgical excision has optimal diagnostic sensitivity and deserves both current consideration and further study as an adjunct to standard antibiotic therapy to improve the otherwise slow response to treatment.

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