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Review Article

CONVENTIONAL AND RECENT DIAGNOSTIC AIDS IN TUBERCULOUS LYMPHADENITIS: A BRIEF OVERVIEW

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ABSTRACT

One of the most common form of extra-pulmonary tuberculosis (TB) is peripheral tuberculous lymphadenitis and accounts for 20-40% of the cases. Tuberculous lymphadenitis has a gender and age predilection (usually seen in young females). It is usually bilateral in presentation and is noncontagious. Recent upsurge in HIV coinfection has challenged the diagnosis and management of TB and of associated lymphadenopathy. In the endemic areas, tuberculous lymphadenitis remains an important and essential differential diagnosis in patients presenting with cervical swellings. A timely and accurate diagnosis is mandatory to overcome this public health threat. Interdisciplinary involvement of varied medical and dental professionals enhances the possibility of an effective and timely diagnosis of this condition.

Keywords: Cervical lymphadenopathy, Diagnosis, Management, Tuberculosis.

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INTRODUCTION

Tuberculosis (TB) is a multisystemic chronic infection caused by *Mycobacterium* TB and characterized by granuloma formation. The primary organ involved is the lungs, although disease other organs and systems may also be affected. 25% of the cases are attributable to extra-pulmonary TB with 10-35% detected in the head and neck region [1,2].

TB of the lymphatic system is the most common extra-pulmonary form of TB, second only to tuberculous pleurisy [3]. Cervical tuberculous lymphadenopathy (LD) accounts to the most frequent cause of persistent cervical lymphadenitis in the developing countries [4].

CLINICAL FEATURES

The predilection for younger age groups and female gender forms the distinguishing features for TB lymphadenitis [5]. The condition usually affects individuals in the age range of 20-40 years [6]. The underprivileged state of women in rural Indian society may be a factor for unusual age and gender distribution [7].

Tuberculous lymphadenitis manifests as a slowly enlarging painless swelling of one or more lymph nodes of weeks to months interval. Systemic symptoms, i.e. fever, weight loss, fatigue and night sweats may occur in patients with extensive disease or coexisting disease. The initial presentation of TB lymphadenitis is firm, discrete, and mobile nodes with free overlying skin. Later, the nodes may become matted with inflamed overlying skin. Softening of the nodes with formation of abscesses and sinus tracts takes place in the advanced stages of the disease. Compression or invasion of the adjoining structures may occur in cases of unusually large nodes, complicating the course of the disease [8].

Jones and Campbell classification for tuberculous lymphadenitis - [9].

- Stage 1 - Reactive lymphadenitis - discrete, enlarged, mobile, ϐirm, nodes with features of nonspeciϐic reactive hyperplasia
- Stage 2 - Periadenitis - Rubbery lymph nodes ϐixed to adjoining tissues
- Stage 3 - Formation of a cold abscess with softened central region
- Stage 4 - Presence of collar-stud abscess
- Stage 5 - Sinus tract formation.

Essential features of a tuberculous sinus are bluish, thin, undermined edges with little clear exudates [10]. Three essential features of tuberculous lymphadenitis are multiple, matted caseating lymph nodes. Often, the LD is bilateral and noncontiguous [11].

The recent upsurge in HIV coinfection has challenged the diagnosis and management of TB and of associated LD.

DIAGNOSIS

In patients presenting with chronic lymph node enlargement, TB should be given the first differential diagnosis [12].

Regardless of recent advances in diagnostic laboratory skills, mycobacterial cervical lymphadenitis still remains a diagnostic dilemma for many clinicians. It is mandatory to differentiate between tuberculous and nontuberculous mycobacterium cervical lymphadenitis as the management strategies varies for the two entities [13].

Table 1 show tuberculous lymphadenitis and nontuberculous lymphadenitis: Differentiating features [12].

1. Age more than 40-50 years. TB lymphadenitis has a predilection for younger age group (20-40 years)
2. Lymphadenitis of the supraclavicular region may be indicative of malignancy
3. No previous history of TB exposure
4. A questionable repeat ϐine needle aspiration cytology (FNAC).
5. Nonreactive montoux test
6. Persistance of clinical symptoms and LD after starting anti-TB therapy (ATT).

Most cases of nonresistant TB LD shows lymph node regression within 2-4 months after initiation of ATT. Lack of resolution after 2 months of starting therapy should highlight the resistant TB or non-TB causes.

Diagnostic aids for tuberculous lymphadenitis can be broadly divided into:

- Primary diagnostic aids
- Ancillary diagnostic aids.

PRIMARY DIAGNOSTIC AIDS

Culture or polymerase chain reaction (PCR) is essential aids for a conclusive diagnosis of tuberculous lymphadenitis [14].

Culture

Mycobacterial culture has been the diagnostic choice for tuberculous lymphadenitis. Culture results may be achieved by the use of various media such as Lowenstein Jenson, Middlebrook, BACTEC TB. Major drawback with the use of culture is its slow growth. (requires at least 4 weeks for mycobacterial growth). Micro colony detection on solid media, septicheck acid fast bacilli (AFB) method, microscopic observation of broth culture, BACTEC 460 radiometric system, BACTEC MGIT 960 system, MB/BacT system and ESP II culture system are some of the recent rapid methods used [15] (Fig. 1).

Smears

Ziehl–Nelson (ZN) staining - ZN staining is an essential diagnostic tool for the identification of AFB and the evaluation of treatment outcome in TB [16]. Bright red rods against blue, green or yellow background are characteristic of AFB [3] (Fig. 2). Major limitations of ZN staining include delayed results, low sensitivity, and use of oil immersion.

Auramine fluorescence - bright rods against dark background are seen with the use of fluorescent microscope [7]. Fluorescent microscopy provides results in a less time and using lower magnifications. Auramine-rhodamine or Papanicolaou staining using fluorescent microscope has been suggested to be advanced aid to ZN staining [17,18] (Fig. 3).

FNAC

FNAC is almost safe, cost-effective and conclusive procedure [19]. It serves as a substitute to excision biopsy for lymph nodes and is an easy procedure for sample collection for cytomorphological and bacteriological examination [20]. FNA cytology has a sensitivity and specificity of 88% and 96%, respectively, in case of tuberculous lymphadenitis diagnosis [21]. The diagnostic accuracy of mycobacterial cervical lymphadenitis may be greatly enhanced when FNAC is used along with culture or a mantoux test [22-24] (Fig. 4).

Excisional biopsy and histopathology The literature has classically supported excisional biopsy as the definitive diagnostic procedure for diagnosis of nodal TB [25,26]. Caseating granulomas with giant cells (langhans and foreign body giant cells) are characteristic for TB. Limitations associated with histopathology are (a) invasive procedure (b) lack of facilities in peripheral health-care centers incisional biopsy is associated with sinus tract and fistula formation, and therefore, is contraindicated [27]. Presently, this technique has been largely replaced by FNAC and histopathology is only reserved for patients with negative FNA despite high clinical suspicion (Fig. 5).

PCR

The PCR has emerged as a significant aid in the diagnosis of *Mycobacterium* TB in developed countries [28]. Its sensitivity ranges between 43% and 84%, and its specificity between 75% and 100% [29,30]. PCR is the test of choice in smear and culture negative cases [31]. PCR outweighs the conventional diagnostic methods because it is highly sensitive, results can be obtained in few hours, provides distinction between *Mycobacterium* TB complex and mycobacterial species other than TB, and identifies drug resistance gene mutations [32,33].

Table 1: Differences between tuberculous and non tuberculous lymphadenitis

	Tuberculous lymphadenitis	Non tuberculous lymphadenitis
Age range (years)	20-40	40-60
Birth country	TB endemic	Non TB endemic
Location	Cervical	Cervicofacial
Pulmonary disease	Common	Absent
Tuberculin skin test	Positive	Occasionally positive
FNAC	FNAC is conclusive	A questionable repeat FNAC
Malignancy	Not indicative	Supraclavicular lymphadenitis is indicative of malignancy
Prognosis	Cessation of clinical symptoms and LD After Starting anti-TB therapy	Persistance of clinical symptoms and LD after starting anti-TB therapy

Fig. 1: Lowenstein Jenson Culture medium showing *Mycobacterium tuberculosis* growth

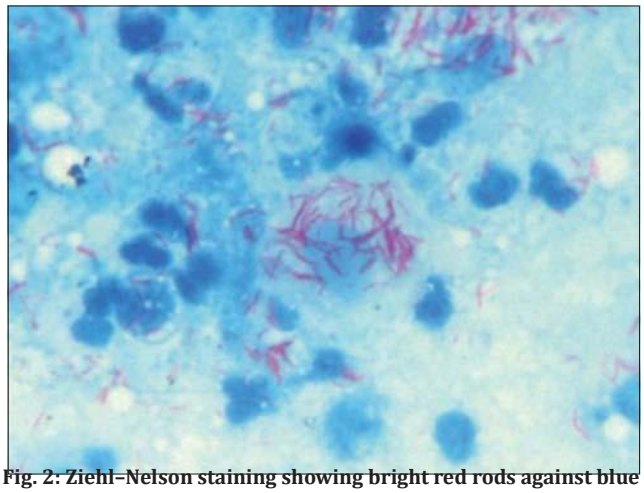

Fig. 2: Ziehl–Nelson staining showing bright red rods against blue background

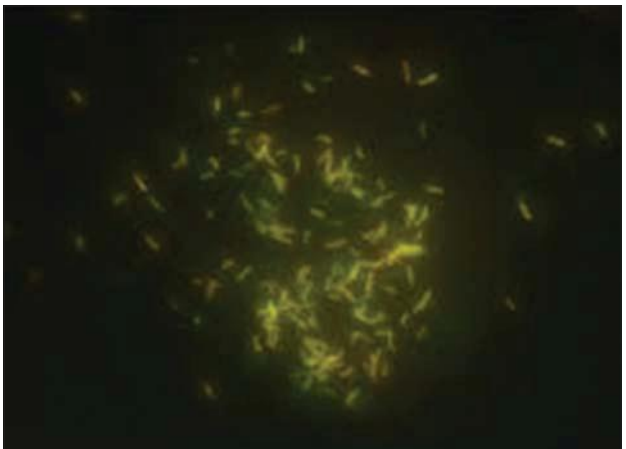

Fig. 3: Auramine-rhodamine staining showing bright rods against dark background

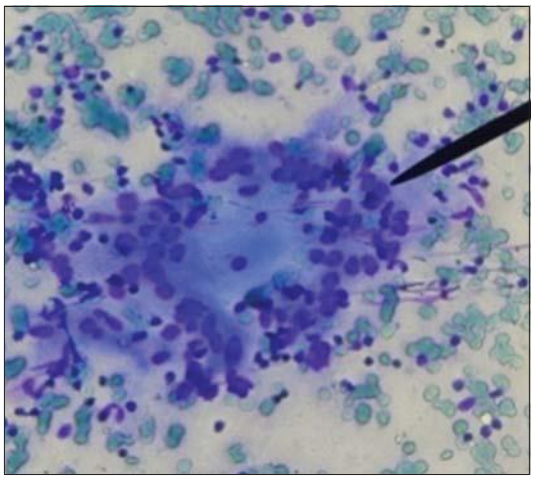

Fig. 4: Fine needle aspiration cytology showing cellular aspirate with giant cells and necrotic debris

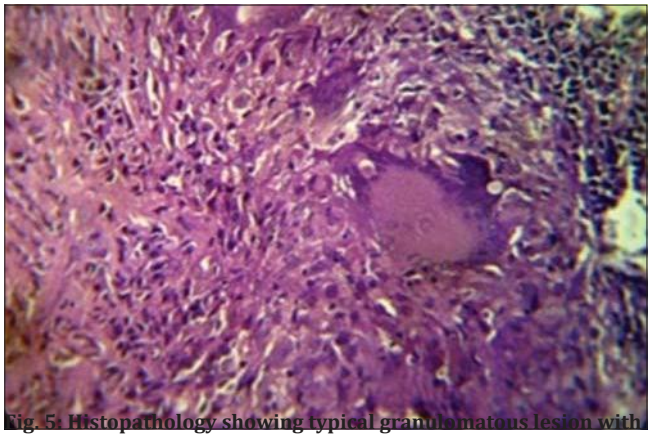

Fig. 5: Histopathology showing typical granulomatous lesion with epitheloid cells and lymphocytes

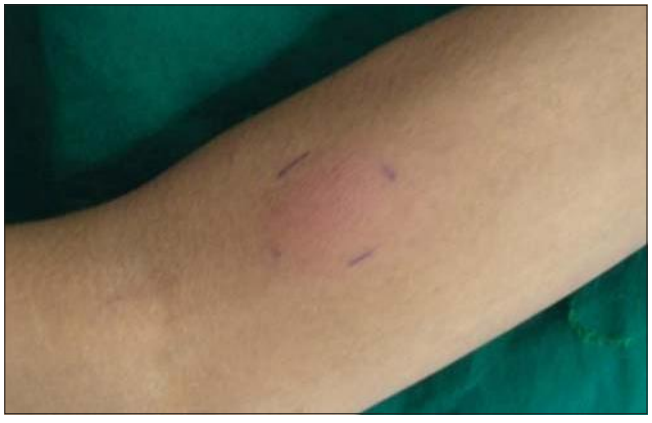

Fig. 6: Induration on the forearm, showing positive tuberculin test

ANCILLARY DIAGNOSTIC TESTS

Tuberculin skin test/mantoux test (TST)

It is an intradermal test that demonstrates a delayed type hypersensitivity reaction against mycobacterial antigen. In general, a protein purified derivative is used as the reagent.

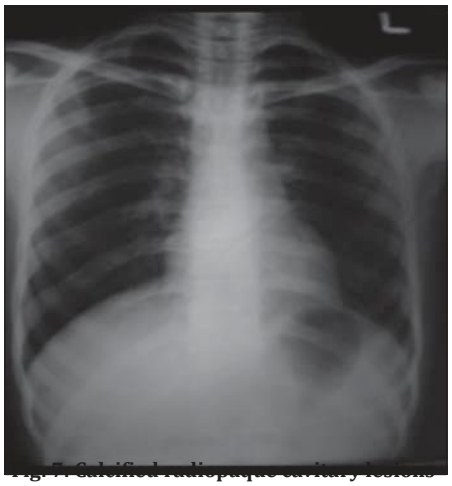

Fig. 7: Calcified radiopaque cavitary lesions

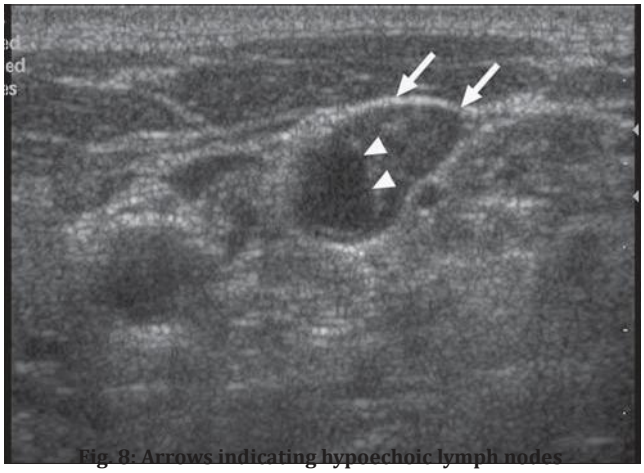

Fig. 8: Arrows indicating hypoechoic lymph nodes

The positive test can be detected after 2-10 weeks of mycobacterial inoculation.

False positive TST reactions may occur in individuals with previous BCG vaccination or nontuberculous mycobacterial infections [31]. Interferon-γ release assays have greater specificity than the TST as they do not show false positive reactions with bacille Calmette-Guérin (BCG) or nontuberculous mycobacteria other than *Mycobacterium marinum*, *Mycobacterium kansasii*, and *Mycobacterium szulgai* [34] (Fig. 6).

Chest radiographs

Chest radiographs may reveal multiple areas of radiolucency (darkened areas), cavities, infiltrates or consolidation in a TB patient [7]. About 10-40% of the patients show positive chest radiograph findings [13] (Fig. 7).

Ultrasound

Ultrasound has been used as a rapid, noninvasive, economical, repeatable, and easily available aid for the assessment of cervical lymph nodes. The cytological and pathological details (by the use of ultrasonography guided FNAC and cervical node biopsy) significantly enhances the diagnostic precision of ultrasound [35]. Neck ultrasound reveals increased edema in the surrounding soft-tissue, homogeneity, matting, intranodal cystic necrosis, and posterior enhancement, along with the appearance of lymph node metastases [13] (Fig. 8).

Computed tomography (CT) and magnetic resonance imaging (MRI)

Exact location and extent of the infection may be demonstrated by CT and MRI. Initially, the nodes appear as enlarged, well-defined lymph nodes with homogenous contrast enhancement. Advanced cases show matting with central low attenuation on CT and iso- or hypointense on T2-weighted imaging [36].

CONCLUSION

Unfortunately, despite several diagnostic aids, TB still remains as one of the leading cause of death from a single infectious organism. About 32% of the global population is infected with TB and an estimated 2 million people die annually from this treatable disease [37]. The launch of the directly observed treatment short-course strategy by the World Health Organization was expected to substantially curb the incidence of TB [38]. However, an increase in the incidence of mycobacterium TB strain resistance or reduced responsiveness to the first line of anti-TB drugs is a major contributory factor to the current spike in the incidence of this epidemic worldwide [39]. Multidrug-resistant tuberculosis (MDR-TB) is defined as bacilli resistant to at least two first-line agents, isoniazid and rifampin. Drug-resistant tuberculosis developed due to improper previous treatment or interruption of tuberculosis treatment. Treatment of multidrug-resistant TB (MDR-TB) is more than 100 times as costly as treatment of drug susceptible TB, difficult, less effective, requiring intensive care management for its prolonged (18-24 months) and more toxic treatment course [40]. A confirmed diagnosis and differential diagnosis usually needs a high level of expertise and application of a variety of diagnostic modalities. Ideally, diagnosis and treatment should be based on the location of the disease and a thorough clinical evaluation depending on the individual. Treatment with antituberculous medication is essential. Surgery may be required in selected cases.

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