Review Article

Nodal tuberculosis revisited: a review

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Abstract

Lymphadenitis is the most common extrapulmonary manifestation of tuberculosis. Tuberculous lymphadenitis is considered to be the local manifestation of the systemic disease, whereas lymphadenitis due to nontuberculous mycobacteria is truly a localized disease. A high index of suspicion is needed for the diagnosis of tuberculous lymphadenitis which is known to mimic a number of pathological conditions. Over the last two to three decades, fine needle aspiration cytology (FNAC) has emerged as a simple out-patient diagnostic procedure for the evaluation of tuberculous lymphadenitis and has replaced lymph node biopsy for histopathology. A number of molecular methods have also been introduced in diagnostics which have greatly improved the diagnostic accuracy. This article provides a review of epidemiology, clinical manifestations, and pathogenesis and emphasizes current trends in pathologic diagnosis of nodal tuberculosis.

Key words: Mycobacterium tuberculosis; lymphadenitis; pathogenesis; diagnosis; fine needle aspiration cytology

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Introduction

Tuberculosis (TB) has been a major cause of suffering and death since time immemorial. Thought to be one of the oldest human diseases, the history of TB is almost as old as mankind [1]. Since the identification of *Mycobacterium tuberculosis* as etiologic agent for tuberculosis by Robert Koch in 1882, there have been great advances in our understanding of many of the crucial aspects in its pathogenesis, but tuberculosis is nowhere near eradication or even control in many regions of the globe [2].

TB is worldwide in distribution, but is particularly more prevalent in Asia and Africa. According to a 2008 World Health Organization (WHO) report, 9.2 million cases were detected and 1.7 million people lost their lives due to TB the world over. India, China, Indonesia, South Africa and Nigeria rank first to fifth respectively in terms of absolute numbers of cases [3]. India has the highest TB burden accounting for one fifth of the global incidence. According to a report issued by the government of India, nearly 40% of the Indian population is infected with the TB bacillus [4].

Primarily considered to be a pulmonary disease, TB can affect almost any organ [5]. The term "extrapulmonary TB" has been used to describe the isolated occurrence of TB at body sites other than the lung. The most common sites of extrapulmonary tuberculosis consist of lymphatic, genitourinary, bone and joint, and central nervous system involvement, followed by peritoneal and other abdominal organ involvement [6].

Isolated peripheral tuberculous lymphadenitis has afflicted mankind for thousands of years. Tuberculous lymphadenitis in the cervical region is known as scrofula, a term derived from the Latin for "glandular swelling." The disease was known as the "King's Evil" in the Middle Ages because of the widespread belief that it could be cured when the affected individual was touched by royalty [7]. There is some evidence to suggest that Clovis, king of the Franks in the 5th century, was the first to practice healing by this method. Edward the Confessor probably introduced the cult into England when he came to the throne in 1042, and for the next 650 years the kings and queens of England and France rivaled each other in their ability to cure this disease. In England the cult reached its height under Charles II. He is reported to have treated 10,000 cases a year with his royal touch [8]. The microbiological cause of scrofula was first appreciated by Bollinger, May and Demme in the mid to late 19th century when they noted that *Mycobacterium bovis* from cows was the cause of this ailment [9].

Epidemiology

An increasing incidence of extrapulmonary TB has been noted both in developing and developed countries since the mid-1980s. Almost one-fifth of TB cases in the United States are extrapulmonary [10]. In India, extrapulmonary TB comprises 20% of all TB cases. Its prevalence in the country varies between 8.3% to 13.1% in different districts according to cohort analysis by the Central TB Division, Ministry of Health and Family Welfare in 2002 [11]. Extrapulmonary TB has become more common since the advent of human immunodeficiency virus (HIV) infection. Extrapulmonary involvement can be seen in more than 50 percent of patients with concurrent AIDS and TB. The risk of extrapulmonary TB and mycobacteremia increases with advancing immunosuppression [12].

In India and other developing countries, tuberculous lymphadenitis continues to be the most common form of extrapulmonary tuberculosis and accounts for 35% of cases [13]. The incidence of tuberculous lymphadenitis has increased in parallel with the increase in the incidence of mycobacterial infection worldwide. Cervical adenopathy is most common, but inguinal, axillary, mesenteric, mediastinal, and intramammary involvement all have been described. According to a study from our hospital, tuberculosis accounted for 60 out of 94 cases (63.8%) of cervical lymph node enlargements between June 1997 and May 1998 [14].

In the developed countries despite the decline in incidence of pulmonary TB, nodal TB still remains an important health issue. However, not much data is available in the literature. According to the German Public Health Organisation, frequency of lymph node TB accounts for 7.5% of all patients infected by *M. tuberculosis*. In another German study, the majority of the cases reported were immigrants of Afghani, Pakistani and Indian origin. In these cases cervical lymph nodes were involved in 63.3% of cases [15].

The tuberculous bacilli that cause disease in humans are usually *Mycobacterium tuberculosis*, *M. bovis* and *Mycobacterium africanum*. Before the widespread pasteurization of milk and the control of TB in cattle, many cases of cervical TB were due to M. bovis. Presently in developing and underdeveloped countries, *M. tuberculosis* is the most common cause of mycobacterial lymphadenitis. Lymphadenitis can also be caused by nontuberculous mycobacteria (NTM). Recent reports have shown that disease caused by NTM is on the rise, and in many developed countries NTM account for an increasing proportion of mycobacterial disease. The distribution of the various NTM is not uniform and appears to be geographically and environmentally dependant. Three of the NTM are known to cause lymphadenitis: *Mycobacterium scrofulaceum*, *Mycobacterium avium-intracellulare* complex, and *Mycobacterium kansaii*. In general, in cases of nontuberculous adenitis, *Mycobacterium avium-intracellulare* complex is the most common causative agent [16].

Over the past 10 years molecular methods have become available to type the strains of *M. tuberculosis*. The TB research community entered the genomic era in 1998 with the publication of the complete annotated genome of *M. tuberculosis* laboratory strain H37Rv. Since then, *M. tuberculosis* clinical strain CDC1551 and six related mycobacteria, *Mycobacterium leprae*, *Mycobacterium ulcerans*, *Mycobacterium avium*, *Mycobacterium avium paratuberculosis*, *Mycobacterium smegmatis* and *M. bovis*, have been fully sequenced. The field of molecular epidemiology has added to our understanding that different strains exhibit specific virulence properties, epidemic potential, and various replication rates [17]. Recent years have witnessed a dramatic upsurge in cases of drug-resistant *Mycobacterium tuberculosis* infections. Various studies have identified different mutations occurring in clinical isolates of *M. tuberculosis*, some of them mutations in the rpoB, katG and ahpC genes [18,19]. These have implications for the control of the organism and prevention of its spread.

Clinical presentation

The unusual features of TB lymphadenitis are its gender and age distribution, as it is more common in females and in the younger age groups, in contrast to pulmonary tuberculosis which is more common in males and in the older age group [20]. It has a peak age of onset of 20 to 40 years [12]. Patients usually present with slowly enlarging lymph nodes which may otherwise be asymptomatic. Some patients may manifest systemic symptoms such as fever, weight loss, fatigue, and occasional night sweats. These symptoms are more commonly seen in HIV positive patients. *M. tuberculosis* commonly involves the jugular, posterior triangle, or supraclavicular lymph nodes [1]. NTM usually occurs in children between one and five years of age [21]. NTM lymphadenitis commonly involves upper cervical lymph nodes, salivary glands, and surrounding nodes. Lymph node enlargement may appear rapidly and may be

associated with fistula formation. Systemic symptoms are not a prominent feature.

Pathogenesis

The pathogenesis of peripheral mycobacterial lymphadenitis is incompletely understood, and there has been persistent debate over the local versus generalized nature of the disease [7].

Tuberculous lymphadenitis is generally thought to be a local manifestation of a systemic disease. The organism, *M. tuberculosis*, usually enters the human body via the respiratory tract and undergoes lymphohematogenous dissemination. Primary infection occurs on initial exposure to tubercle bacilli. The bacilli lodge in terminal alveoli of lungs and multiply there forming the Ghon's focus. The lymphatics drain the bacilli engulfed by macrophages to the hilar and mediastinal lymph nodes and this forms the primary complex [22]. Peripheral lymphadenitis may occur at the time of initial infection (as seen in young children and immunocompromised patients) or may reflect a reactivation of a prior primary infection [23].

Yew *et al*. [24] suggested that the predominant pathway of spread of the tubercle bacilli to the cervical lymph nodes is from lung parenchyma as the lymphatics of the right lung and the lower lobe of the left lung normally drain to the right supraclavicular lymph nodes and then upwards to the right lower cervical chain. In this study, chest radiographs showed that 41.4% of patients with tuberculous lymphadenitis had evidence of pulmonary tuberculosis, and 22.5% of these had radiographically active disease.

However, the pathogenesis of tuberculous lymphadenitis cannot be totally explained by parenchymal lung diseases, and alternate routes of spread to lymph nodes, such as the tonsils and adenoids, have been proposed [25-27]. Other members of Waldeyer's ring, and occasionally carious teeth, middle ear and mastoid, could also affect the regional lymph nodes [8].

NTM is primarily a disease of childhood. NTM are ubiquitous in soil and water and are also carried by animals and birds. Humans usually acquire these organisms from environmental sources. In contrast to tuberculous lymphadenitis, NTM appears to be truly a localized disease, and the pathogens usually enter the lymph nodes directly via oropharyngeal mucosa, salivary glands, tonsils, gingiva or conjunctiva. This feature is particularly important in children because deciduous teeth may harbor the NTM that may reach the neck sites around the mandible through the lymphatics [28].

Tuberculous lymphadenitis is thus considered a component of systemic tuberculous disease, treatable with medical therapy. NTM, on the other hand, is considered a localized disease in which surgery has an important role in treatment [29].

The range of lesions that are observed in nodal tuberculosis is the result of a continuous interaction between bacterial virulence and individual response. The bacilli get lodged in the sinuses of the lymph nodes where they form typical tubercles. Cytokines and lymphokines liberated by the destroyed macrophages result in accumulation of monocytes and macrophages. At this early stage of tuberculous lesion, there is little cell death or tissue necrosis and tubercle bacilli multiply within the accumulated macrophages. After two to four weeks, macrophages of the host develop an increased ability to destroy bacilli contained within, while simultaneously many of the macrophages begin to be killed by the bacilli or their byproducts. It is at this stage that the tubercle forms a caseous center (from the Latin *caseus*, meaning cheese), which contains necrotic tissue centrally, while granulation tissue containing viable macrophages and their modified form as epithelioid cells, lymphocytes, and other cells is formed peripherally [22]. Initially, the nodes are discrete. Periadenitis results in matting and fixation of the lymph nodes and may break down due to formation of caseous pus. This may perforate the deep fascia and present as a collar-stud abscess. Overlying skin becomes indurated and may result in sinus formation. When healing occurs, it is associated with calcification and scarring [13].

Diagnosis

Tuberculous lymphadenitis remains both a diagnostic and therapeutic challenge because it mimics other pathological processes and yields inconsistent physical and laboratory findings. A high index of suspicion is needed for accurate diagnosis. The differential diagnosis of isolated peripheral tuberculous lymphadenitis includes adenitis due to other mycobacteria, bacterial adenitis, fungal disease, toxoplasmosis, sarcoidosis, cat-scratch disease, cystic hygroma, nonspecific hyperplasia, and primary or metastatic neoplasms [7]. A number of diagnostic techniques are available for diagnosis of tuberculosis. Over the last few years, there has been a changing trend and improved diagnostic approach to nodal TB.

Histopathology

The literature has classically supported excisional biopsy as the definitive diagnostic procedure for diagnosis of nodal TB [7,30]. Identification of caseating granulomatous inflammation with Langhans and foreign body giant cells supports a diagnosis of TB. Though histopathology is most rewarding for diagnosis of cervical lymphadenitis, its feasibility is limited due to lack of facilities in peripheral health-care centers and its non-acceptability, as it is an invasive procedure. Incisional biopsy is associated with sinus tract and fistula formation and therefore is contraindicated [31]. Presently, this technique has been largely replaced by fine needle aspiration cytology (FNAC) and histopathology is only reserved for patients with negative FNA despite high clinical suspicion.

Fine needle aspiration cytology

FNAC is a simple, less expensive out-patient diagnostic procedure used for the diagnosis of tuberculous lymphadenitis [32]. FNA has excellent sensitivity and specificity for the diagnosis of mycobacterial lymphadenitis and is recommended to be used as the initial diagnostic test in suspected cases.

The following cytomorphological patterns can be seen in FNA smears from a suspected case of nodal tuberculosis [33]:

1. Predominantly reactive picture with occasional or a few clusters of epithelioid cells. In such cases, the diagnosis may be missed unless a diligent search of all the smears under low-power followed by high-power microscopy is made for clusters of epithelioid cells.
2. Presence of numerous clusters of eptihelioid cells (Figure 1) with presence of multinucleate giant cells (Figure 2). In this pattern the diagnosis can be made with relative ease.
3. Mostly necrotic material, with a few epithelioid cells found on diligent search (Figure 3).
4. Mostly necrotic material with a few lymphocytes and histiocytes but no epithelioid cells.
5. Necrotic material only.

In a recent report from this department [34], the cytomorphological features of tuberculosis in fine needle aspirates of lymph nodes were analyzed. Out of 36 cases which had cytological features of tuberculous lymphadenitis, a combination of well-formed epithelioid cell granulomas, giant cells and caseous necrosis was seen in 17 cases (34%), epithelioid cell granulomas but no caseous necrosis was seen in 6 cases (12%), and only caseous necrosis unassociated with granulomas was seen in 13 cases (26%).

A confident diagnosis of TB can be rendered on cytology when a combination of epithelioid cell granulomas and caseous necrosis with or without multinucleated giant cells is seen. However, typical granulomas and caseation are less likely to be found in tuberculous lymphadenitis in advanced HIV disease because T-cell functions are necessary for epithelioid granuloma formation. Instead, necrotizing atypical granuloma formation is a pattern consistent with advanced HIV disease [35]. The presence of microabscesses, ill-defined granulomas, non-caseating granulomas and a small number of giant cells is more prominent in NTM adenitis when compared with tuberculous adenitis [36].

Aspirated material is always subjected to Ziehl-Neelsen (ZN) staining for acid fast bacilli (AFB) (Figure 4), mycobacterial culture, and sensitivity testing. Polymerase chain reaction (PCR) analysis of FNA aspirates is a promising technique that allows identification and genotyping of *M. tuberculosis* when only a small amount of sample is obtained.

Microscopy using ZN staining procedure is rapid, cheap and easy. The sensitivity varies depending on the source of the sample. Sensitivity ranges from 46-78% and the specificity is virtually 100% [37]. Sensitivity and specificity of AFB on aspirate smear from lymph nodes in a study in our department was found to be 76.47% and 100% respectively [34]. Centrifugation and fluorochrome staining with ultraviolet microscopy markedly increases the sensitivity of microscopy [38]. AFB yield is highest in the smears in which purulent material is aspirated, as was seen in another study in our department [39].

Culture

Isolation of mycobacteria by culture still represents the cornerstone on which the definitive diagnosis is based. Major constraint of culturing mycobacteria in conventional media is its slow growth, which necessitates a mean incubation period of at least four weeks. Although a combination of solid and liquid media is currently the gold standard for primary isolation of mycobacteria, a few modern rapid methods are also available. These include

Figure 1. Photomicrograph showing epithelioid cell granulomas in a background of reactive lymphoid cells (MGG, X200)

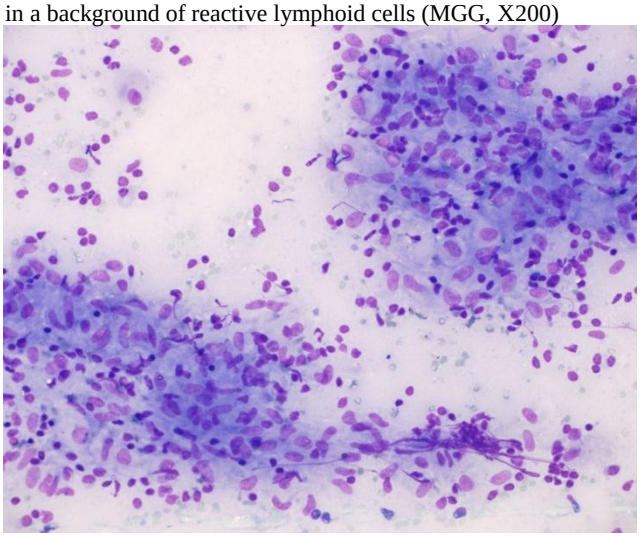


Figure 2. Aspirate smear from tubercular lymph node showing multinucleate giant cell (MGG, X400)

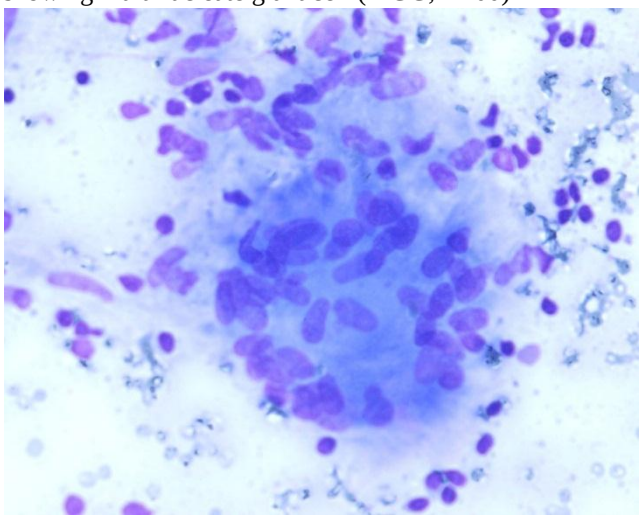


Figure 3. Aspirate smear showing epithelioid cell granuloma in a background of necrosis (H&E, X200)

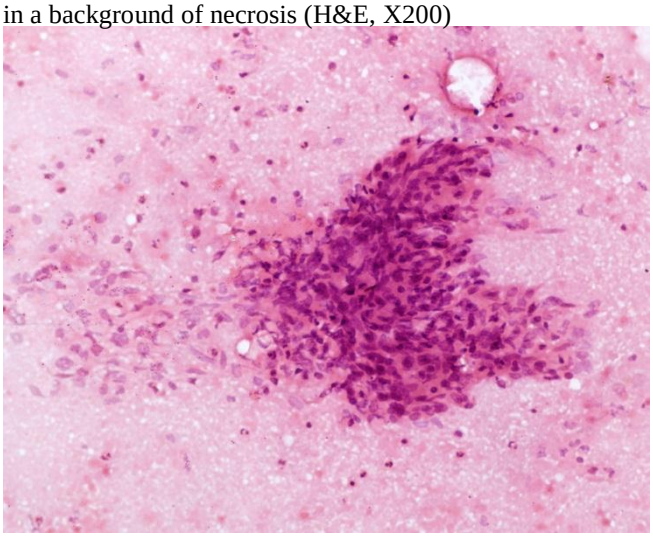
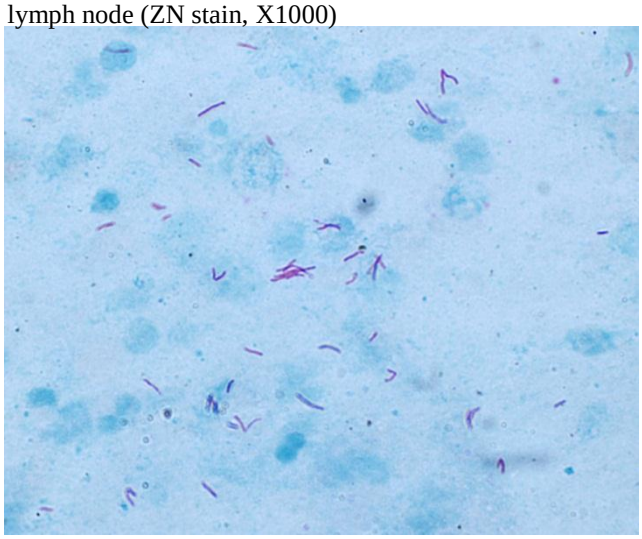


Figure 4. Highly positive AFB smear from tuberculous lymph node (ZN stain, X1000)



microcolony detection on solid media, septicheck AFB method, microscopic observation of broth culture, the BACTEC 460 radiometric system, BACTEC MGIT 960 system, MB/BacT system and ESP II culture system [40].

Molecular tests

Methods for the diagnosis of TB have improved in recent years with introduction of several molecular techniques in diagnostics [41]. They have much higher sensitivity than conventional methods and results are available within 24 to 48 hours. An early diagnosis allows prompt and specific antimycobacterial treatment. An additional advantage of molecular methods is the direct identification of the species and detection of drug resistance. Polymerase chain reaction (PCR) is a fast and useful technique for the demonstration of mycobacterial DNA fragments in patients with clinically suspected mycobacterial lymphadenitis. The most common target used in PCR is IS6110. Species specific and genus specific PCR methods are being used with various targets and modifications of PCR such as ligase chain reaction, transcription mediated amplification, strand displacement amplification (SDA), nucleic acid sequence based amplification (NASBA), branched DNA (b-DNA) and line probe assay (LiPA) [40].

Tuberculin test

This intradermal test (Mantoux test) is used to show delayed type hypersensitivity reactions against mycobacterial antigens, in which the reagent is mostly protein purified derivative (PPD). Positive reactions (> 10mm induration) can occur in *M. tuberculosis* infection. Intermediate reactions (5 to 9 mm induration) can occur after BCG vaccination, *M. tuberculosis* or nontuberculous mycobacterial infections. Negative reaction (< 4 mm induration) represents a lack of tuberculin sensitization [42]. The tuberculin test is positive in about 75% patients with lymph node TB while it is often non-reactive in patients with NTM lymphadenitis. More recently, interferon-gamma release assays have become available and may be useful in the diagnosis of TB infection [1].

Imaging modalities

Chest radiograph, ultrasound, computerized tomography and magnetic resonance imaging CT, and MRI of neck can be performed in tuberculous lymphadenitis. Associated chest lesions can be identified by these methods. The status of the retroperitoneal, porta hepatic or mesenteric lymph nodes also can be assessed.

To conclude, a high index of suspicion, detailed history, thorough clinical examination, along with appropriate diagnostic tests, can help in securing the definitive diagnosis of tuberculous lymphadenitis. It is equally important to distinguish between tuberculous lymphadenitis and NTM lymphadenitis as the treatment modalities are different.

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