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TUBERCULAR LYMPH NODE –AN UPDATE

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INTRODUCTION

Tuberculosis, one of the oldest diseases known to affect humans, is caused by bacteria belonging to the Mycobacterium tuberculosis complex.The disease remains a major global public health problem. It is estimated that about one-third of the world's population is infected with Mycobacterium tuberculosis. There were an estimated 8 million new cases of TB, resulting in 1.9 million deaths, with the greatest burden of disease in developing nations [1–3].The disease usually affects the lungs, although in up to one third of cases other organs are involved. If proper treated, tuberculosis caused by drug susceptible strains is curable in virtually all cases. If untreated, the disease may be fatal within 5 years in more than half of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious tuberculosis.War, famine, homelessness, and a lack of medical care all contribute to the increasing incidence of tuberculosis among disadvantaged persons. Since TB is easily transmissible between persons, then the increase in TB in any segment of the population represents a threat to all segments of the population. This means that it is important to institute and maintain appropriate public health measures, including screening, vaccination (where deemed of value), and treatment. A laxity of public health measures will contribute to an increase in cases. Failure of adequate treatment promotes the development of resistant strains of tuberculosis

ETIOLOGIC AGENT

Mycobacteria belonging to the family mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the M.tuberculosis complex, the most frequent and important agent of human disease is M.tuberculosis. The genus Mycobacterium consists of nonmotile, non-spore-forming aerobic acid-fast bacilli. The cell wall is lipophilic and resistant to many disinfectants as well as to common laboratory stains. The complex includes M.bovis, M.africanum, M.microti(vole bacillus),and M.canettii. Tuberculosis infection can be of pulmonary or extrapulmonary type. After primary infection, TB may reactivate at anytime and anywhere in the body. Recent studies have suggested that the sites of extrapulmonary tuberculosis are lymph nodes in the neck, the bones, the serous membranes, and the cervical region. Tuberculosis of the lymphatic system is one of the most common of all extrapulmonary tuberculosis [1,4,5] The synergy between tuberculosis and HIV infection and other immune-compromising conditions have resulted in an increase in the incidence of tuberculosis lymphadenitis and have further

complicated tuberculosis control. HIV-related extrapulmonary tuberculosis is a World Health Organization (WHO) clinical stage four diagnosis, and patients with HIV-related extrapulmonary tuberculosis often have disseminated disease and are at high risk of rapid clinical deterioration and death [6,7].Tuberculosis lymphadenitis occurs relatively early after primary infection with M. tuberculosis and often affects young people in countries with a high prevalence of tuberculosis. In children, the most serious forms are disseminated tuberculosis and tuberculosis meningitis. Tuberculosis lymphadenitis is the most common form, accounting for up to 50 percent of extrapulmonary cases in children [8,9]. Many studies of tuberculous lymphadenitis do not report speciation of the causative organism in the *M. tuberculosis* complex. *M. bovis* was historically a common cause of tuberculous lymphadenitis, but pasteurization and bovine tuberculosis programs have virtually eliminated this source of human infection in developed countries; risk remains with consumption of unpasteurized milk [10]. *M. tuberculosis* is the usual cause of tuberculous lymphadenitis. Other infectious causes of chronic lymphadenitis include nontuberculous mycobacteria(including *M.scrofulaceum,M.avium,* and *M. haemophilum*), *Toxoplasma* species,*Ba rtonella* species, and fungi. Noninfectious causes include neoplasms, sarcoidosis, Castleman disease, drug reactions, and nonspecific reactive hyperplasia

EPIDEMIOLOGY

Peripheral tuberculous lymphadenitis—previously termed "scrofula"—is a unique manifestation of disease due to organisms of the *Mycobacterium tuberculosis* complex. 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 [11]. 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 [12]. 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. 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 [13]. 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. In India and other developing countries, tuberculous lymphadenitis continues to be the most common form of extrapulmonary tuberculosis and accounts for 35% of cases. 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. 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..Primarily considered to be a pulmonary disease, TB can affect almost any organ. 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

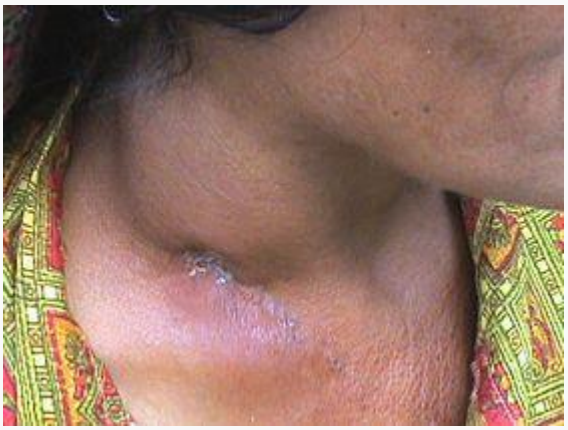
other abdominal organ involvement. Epidemiologic characteristics of t.b.lymph node include a 1.4:1 female-to-male ratio, a peak age range of 30–40 years, and dominant foreign birth, especially East Asian. Patients present with a 1–2 month history of painless swelling of a single group of cervical lymph nodes. Epidemiologic characteristics differ from those of pulmonary tuberculosis, clinical manifestations are variable, and diagnosis may be challenging. A consistent observation in studies from nonendemic countries is that immigrants from Southeast Asia and India appear to have a special predilection for tuberculous lymphadenitis. Although diabetes mellitus is a risk factor for pulmonary tuberculosis, studies suggest that it may reduce the relative risk of tuberculous lymphadenitis. In a review of extrapulmonary tuberculosis in the United States, traditional risk factors for pulmonary tuberculosis, such as homelessness and excess alcohol use, were associated with a lower risk of disease.

PATHOGENESIS

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 .The interaction of M.tuberculosis with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually<10%) reach the alveoli. There, non specifically activated alveolar macrophages ingest the bacilli. Invasion of macrophages by mycobacteria may result in part from association of C2a with the bacterial cell wall followed by C3b opsonization of the bacteria and recognition by the macrophages. The balance between the bactericidal activity of the macrophage and the number and virulence of the bacilli (with virulence partially linked to the bacterium lipid cell wall and to its glycolipid capsule, both of which confer resistance to complement and free radicals of the phagocyte) determines the events following phagocytosis. Several genes thought to confer virulence to M.tuberculosis have been identified, katG encodes for catalage, an enzyme protective against oxidative stress, rpoVis the main sigma factor initiating transcription of several genes. Defects in these two genes result in loss of virulence. These rpgene, encoding a protein required for multiplication,also contributes to virulence. There are two major patterns of disease with TB:

- Primary tuberculosis: seen as an initial infection, usually in children. The initial focus of infection is a small subpleural granuloma accompanied by granulomatous hilar lymph node infection. Together, these make up the Ghon complex. In nearly all cases, these granulomas resolve and there is no further spread of the infection.
- Secondary tuberculosis: seen mostly in adults as a reactivation of previous infection (or reinfection), particularly when health status declines. The granulomatous inflammation is much more florid and widespread. Typically, the upper lung lobes are most affected, and cavitation can occur.

When resistance to infection is particularly poor, a "miliary" pattern of spread can occur in which there are a myriad of small millet seed (1-3 mm) sized granulomas, either in lung or in other organs



Tubercular adenitis with sinus

Tuberculous lymphadenitis (or **tuberculous adenitis**) is a chronic specific granulomatous inflammation of the lymph node with caseation necrosis, caused by infection with *Mycobacterium tuberculosis* or *Mycobacterium bovis*.

The characteristic morphological element is the tuberculous granuloma (caseating tubercule). This consists of giant multinucleated cells and (Langhans cells), surrounded by epithelioid cells aggregates, T cell lymphocytes and fibroblasts. Granulomatous tubercules eventually develop central caseous necrosis and tend to become confluent, replacing the lymphoid tissue.
Stages of tubercular lymphadenitis:

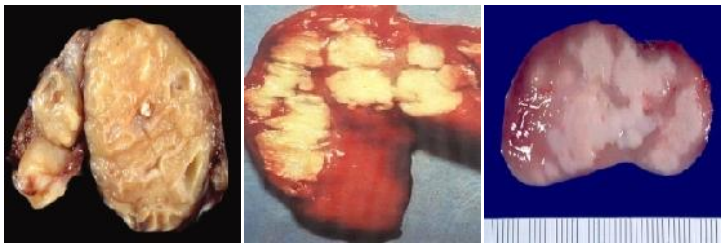
1. Lymphadenitis
2. Periadenitis
3. Cold abscess
4. 'Collar stud' abscess
5. Sinus

Tuberculous lymphadenitis is popularly known as collar stud abscess, due to its proximity to the collar bone and superficial resemblance to a collar stud, although this is just one of the five stages of the disease. The characteristic morphological element is the tuberculous granuloma (caseatingtubercule): giant multinucleated cells (Langhans cells), surrounded by epithelioid cells aggregates, T cell lymphocytes and few fibroblasts. Granulomatous tubercules evolve to central caseous necrosis and tend to become confluent, replacing the lymphoid tissue.

SIGNS AND SYMPTOMS

The most usual signs and symptoms are the appearance of a chronic, painless mass in the neck, which is persistent and usually grows with time. The mass is referred to as a "cold abscess", because there is no accompanying local color or warmth and the overlying skin acquires a violaceous (bluish-purple) color. NTM infections do not show other notable constitutional symptoms, but scrofula caused by tuberculosis is usually accompanied by other symptoms of the disease, such as fever, chills, malaise and weight loss in about 43% of the patients. As the lesion progresses, skin becomes adhered to the mass and may rupture, forming asinus and an open wound.

Pathology–Gross finding-Large multinodular mass that resembles carcinoma with multiple foci of caseous necrosis

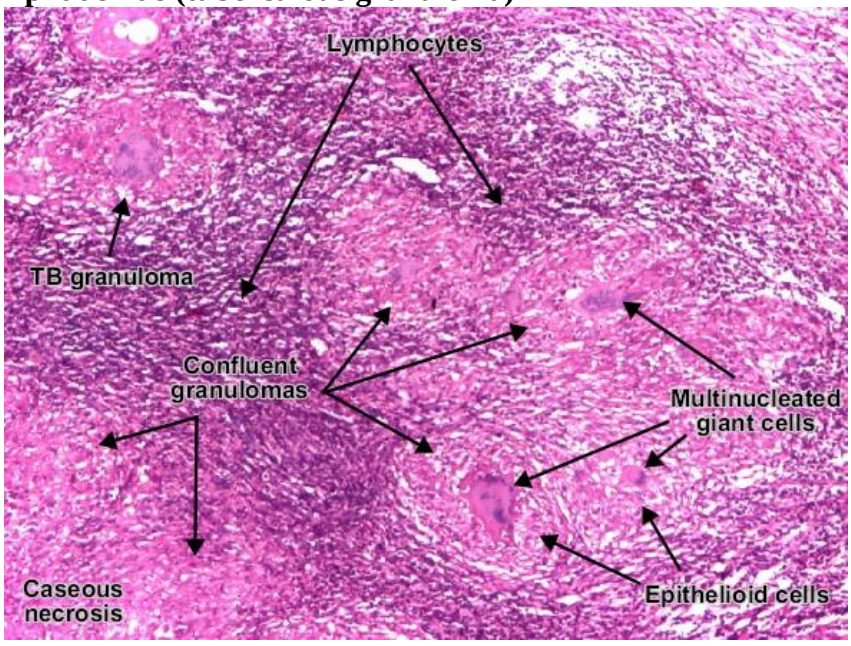


MICROSCOPY

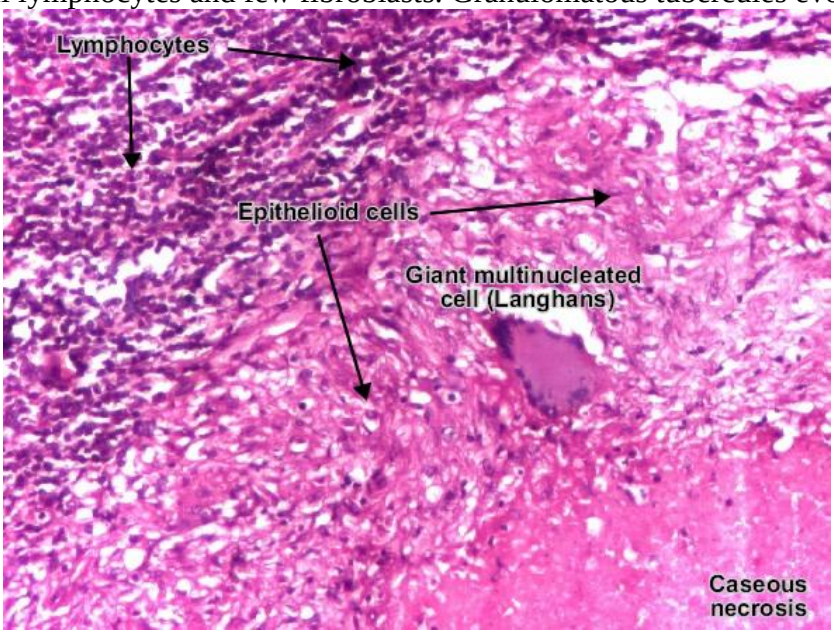
The classical histological pattern of scrofula features caseating granulomas with central acellular necrosis (caseous necrosis) surrounded by granulomatous inflammation withmultinucleated giant cells. Although tuberculous and non tuberculous lymphadenitis are morphologically identical, the pattern is somewhat distinct from other causes of bacterial lymphadenitis [14]. The inflammatory response is mediated by a type IV hypersensitivity reaction. This can be utilized as a basis for diagnosis by a TB skin test. An acid fast stain (Ziehl-Neelsen or Kinyoun's acid fast stains) will show the organisms as slender red rods. An auramine stain of the organisms as viewed under fluorescence microscopy will be easier to screen and more organisms will be apparent. The most common specimen screened is sputum, but the histologic stains can also be performed on tissues or other body fluids. Culture of sputum or tissues or other body fluids can be done to determine drug sensitivities.

1. Granulomas in lung, low power microscopic.
2. Granuloma with caseous necrosis, high power microscopic.
3. Granuloma with epithelioid macrophages and a Langhans giant cell, high power microscopic.
4. Granulomatous endometritis, high power microscopic.
5. Ziehl-Neelsen acid fast stain, microscopic, AFB stain.
6. Auramine stain, M. tuberculosis, fluorescence microscopy.

Tuberculous lymphadenitis (tuberculous granuloma)



Tuberculous lymphadenitis is a chronic specific granulomatous inflammation with caseation necrosis. The characteristic morphological element is the tuberculous Granuloma (caseatingtubercule) : giant multinucleated cells (Langhans cells), surrounded by epithelioid cells aggregates, T cell lymphocytes and few fibroblasts. Granulomatous tubercules evolve to central



Tuberculous granuloma. *Multinucleated giant cell* (mature - Langhans type): 50 - 100 microns, numerous small nuclei (over 20) disposed at the periphery of the cell (crown or horseshoe), abundant eosinophilic cytoplasm. It results when activated macrophages merge. *Epithelioid cells* are activated macrophages resembling epithelial cells: elongated, with finely granular, pale eosinophilic (pink) cytoplasm and central, ovoid nucleus. They have indistinct shape contour and form aggregates. At the periphery are the *lymphocytes (T cells)* and rare plasma cells and fibroblasts. *Caseous necrosis* is a central area, amorphous, finely granular, eosinophilic (pink). If recent, it may contain nuclear fragments. The caseum is the result of giant cells and epithelioid cells destruction. (Hematoxylin-eosin, ob. x20)

FNA has emerged as a first-line diagnostic technique, especially in tuberculosis-endemic countries, where the test is both sensitive and specific [15,16]. 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). Aspiration of superficial enlarged lymph nodes was performed free hand using a 23 G needle mounted on a Cameco handle. Both air-dried and wet-fixed slides were prepared. The air-dried smears were immediately stained with Speedy-Diff (Clin-tech) and the adequacy of diagnostic material assessed. Results of FNAC were available on the day of examination. Granulomata are recognized cytologically by observing aggregates of histiocytes with, and without, associated multinucleated giant cells. (figures 1 & 2) A dirty necrotic background would suggest caseation and possibly tuberculosis. In cases where an infective aetiology was thought likely, needle washings were sent for bacteriological culture and sensitivity. If TB was suspected, an additional sample was sent for culture and slides were also stained with auramine-rhodamine or Ziehl-Neelsen methods to detect acid fast bacilli (AFB) directly.

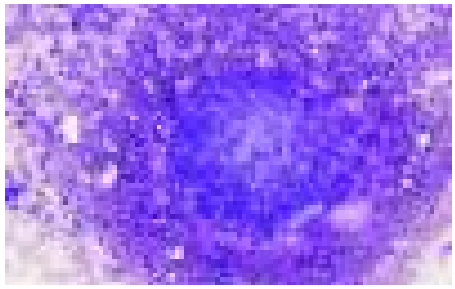


Fig 1 Granuloma formation as seen on fine needle aspirate

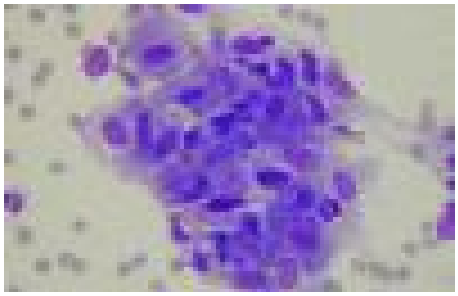


Fig 2 Granuloma-loose aggregates of epithelioid histiocytes

Dissemination of tuberculosis outside of lungs can lead to the appearance of a number of uncommon findings with characteristic patterns:

Skeletal Tuberculosis: Tuberculous osteomyelitis involves mainly the thoracic and lumbar vertebrae (known as Pott's disease) followed by knee and hip. There is extensive necrosis and bony destruction with compressed fractures (with kyphosis) and extension to soft tissues, including psoas "cold" abscess.

Genital Tract Tuberculosis: Tuberculous salpingitis and endometritis result from dissemination of tuberculosis to the fallopian tube that leads to granulomatous salpingitis, which can drain into the endometrial cavity and cause a granulomatous endometritis with irregular menstrual bleeding and infertility. In the male, tuberculosis involves prostate and epididymis most often with non-tender induration and infertility.

Urinary Tract Tuberculosis: A "sterile pyuria" with WBC's present in urine but a negative routine bacterial culture may suggest the diagnosis of renal tuberculosis. Progressive destruction of renal parenchyma occurs if not treated. Drainage to the ureters can lead to inflammation with ureteral stricture.

CNS Tuberculosis: A meningeal pattern of spread can occur, and the cerebrospinal fluid typically shows a high protein, low glucose, and lymphocytosis. The base of the brain is often involved, so that various cranial nerve signs may be present. Rarely, a solitary granuloma, or "tuberculoma", may form and manifest with seizures.

Gastrointestinal Tuberculosis: This is uncommon today because routine pasteurization of milk has eliminated Mycobacterium bovis infections. However, M. tuberculosis organisms coughed up in sputum may be swallowed into the GI tract. The classic lesions are circumferential ulcerations with stricture of the small intestine. There is a predilection for ileocecal involvement because of the abundant lymphoid tissue and slower rate of passage of lumenal contents.

Adrenal Tuberculosis: Spread of tuberculosis to adrenals is usually bilateral, so that both adrenals are markedly enlarged. Destruction of cortex leads to Addison's disease.

Scrofula: Tuberculous lymphadenitis of the cervical nodes may produce a mass of firm, matted nodes just under the mandible. There can be chronic draining fistulous tracts to overlying skin. This complication may appear in children, and Mycobacterium scrofulaceum may be cultured.

Cardiac Tuberculosis: The pericardium is the usual site for tuberculous infection of heart. The result is a granulomatous pericarditis that can be hemorrhagic. If extensive and chronic, there can be fibrosis with calcification, leading to a constrictive pericarditis. Diagnosis is usually performed by needle aspiration biopsy or excisional biopsy of the mass and the histological demonstration of stainable acid-fast bacteria in the case of infection by *M. tuberculosis* (Ziehl-Neelsen stain), or the culture of NTM using specific growth and staining techniques.However, of note, in majority of FNA studies from these regions, the diagnosis of tuberculosis was based on detection of granulomatous inflammation (GI).The diagnosis of LTBI is established by a positive result on either a tuberculin skin test (TST) or an interferon-γ (IFN-γ) release assay (IGRA), in the absence of active TB. Active TB is diagnosed on the basis of a combination of epidemiological (eg, exposure, travel to or residence in a high prevalence area, previous TB), clinical (eg, cough lasting longer than 2-3 weeks, fever, night sweats, weight loss), radiographic (eg, infiltrates, fibrosis, cavitation), microbiological (eg, positive sputum smear or culture), and histopathologic (eg, caseating granuloma) features

TREATMENT

Treatments are highly dependent on the kind of infection. Surgical excision of the scrofula does not work well for *M. tuberculosis* infections, and has a high rate of recurrence and formation of fistulae. Furthermore, surgery may spread the disease to other organs. The best approach is to use conventional treatment of tuberculosis withantibiotics. The cocktail-drug treatment of tuberculosis (and inactive meningitis) includes rifampicin alonewith pyrazinamide, isoniazid, ethambutol,and streptomycin ("PIERS"). Scrofula caused by NTM, on the other hand, responds well to surgery, but is usually resistant to antibiotics. The affected nodes can be removed either by repeated aspiration, curettage or total excision (with the risk in the latter procedure, however, often causing unsightly scarring, damage to the nerve or both.

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