Chapter 5
Lymphatic Tuberculosis

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5.1 Epidemiology

Formerly, since Hippocrates, the terms ‘scrofula’ or ‘king’s evil’ stood for all cervical lymph node swellings. Upon the discovery of tubercle bacillus in 1882, the causative agents for lymph node diseases became to be distinguished, and cases due to *Mycobacterium tuberculosis* are named as glandular tuberculosis. Moreover, it was determined that *Mycobacterium tuberculosis* was not the only causative agent for lymph node diseases.

Lymphadenitis due to tubercle bacilli was seen mostly among children and assumed to be a childhood manifestation of tuberculosis. Müller George P shared one of the earliest available statistical reports over tuberculous lymphadenitis (TL) and noted the peak incidence age group as 2–17 years old [21]. In time, until the 1970s, with the rise of the awareness of preventive measures, the overall incidence of tuberculosis decreased. William C Voorsanger stated in 1937 that the death rate from tuberculosis decreased from 325 per 1,000,000 to 58 and the main decline took place in the age group of 1–10 years in which TL was most common [42]. Though, especially since the 1970s, synchronously with the rapid spread of HIV infection, the average incidence interval for TL changed from childhood to 20–40 years [30]. The rise of the haematological malignancies and the use of immunosuppressant medications to prevent rejections in solid organ transplantations also contributed to the rise of tuberculosis and its complications within the adult age group. Ilgazli et al., in a study, consisted 636 cases with ages from 1 year to 89 years, found that the mean age for EPTB cases was 22.5 [17]. The result of another study performed by Mihai Raul POPESCU demonstrated a mean age of 35 years among 362 EPTB cases [32]. Muluye et al. from Northwest Ethiopia published the highest prevalence of TL within the age group of 15–24 and followed by the age group of 25–34 years [25].

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Mycobacterium tuberculosis complex is the main cause of TL and consisted of a group of microorganisms [15]. *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium canettii* are the bacteria in this group. Although the main target of mycobacteria is the lung, the bacilli may spread out from the lungs to other organ and tissues during the active phase or reactivation of the latent disease and form extrapulmonary tuberculosis (EPTB), and TL is the most common EPTB manifestation. Additionally, bovine tuberculosis agent *Mycobacterium bovis* and a variety of nontuberculous mycobacteria may infect especially cervical lymph nodes when contaminated dairy products consumed without pasteurisation.

Study	Period	No of cases	LN involvement %
Frossbohm et al. (2008) [48]	1996–2000	5675	39.8
Chan-Young et al. (2002) [49]	1996	1283	36.5
CDC [50]	2007	2697	42.5
Chandir et al. [8]	2005–2007	194	35.6
Rodriguez et. al. [33]	2003–2008	146	34.9
Popescu et al. [32]	1990–2012	732	49.45

In the surveillance report for tuberculosis in 2016, the US centre for disease control [6] indicates percentages of pulmonary, extrapulmonary and both pulmonary-extrapulmonary cases has been increased as 69.6 %, 20.3 % and 9.9 %, respectively, throughout the USA. The report also indicates the lymphatic tissue is the most common extrapulmonary destination for tuberculosis with a high percentage of 35.8% among in all extrapulmonary tissues affected by mycobacteria. Tuberculous lymphadenitis may infect all the lymphatic tissue, but the most common infected site is the cervical lymphatic region.

Not only the coexisting diseases but the burden of the infection across the geography has a great impact on the statistical data. In high-burden countries, extrapulmonary tuberculosis rates are reported to be higher. WHO Global tuberculosis report in 2017, demonstrates percentages of extrapulmonary tuberculosis rates as global and WHO regions Africa, The Americas, Eastern Mediterranean, Europe, Southeast Asia, Western Pacific as 15%, 16%, 15%, 24%, 15%, 15% and 8%, respectively. The European centre for disease control [12] 2013 report points out a percentage of 22.3% extrapulmonary tuberculosis cases across EU, while the US [6] report notes a percentage of 30.2% extrapulmonary tuberculosis cases across the USA. Another author Teresa Gomes et al. reported an overall 17% of EPTB in Brasil between the years 2007 and 2011 [14].

Gender and place of origin also play an important role in the development of TL. Although tuberculosis is more common in males, EPTL is more common in females. Statistical reports usually demonstrate female to male ratio as 1.4:1. In a study in Romania including a large number of cases, Mihai Raul Popescu reported a ratio of male/female TL cases as 0.63 [32]. In addition, Popescu indicated that patients with only TL were more likely to be women despite the fact that patients with TL and additional tissue infection were mostly men.

Living in high-burden or low-burden areas and social-economical conditions affect not only tuberculosis and EPTB but also TL rates as well. T. Gow Brown discussed the effects of living in an unhealthy environment and stated all manifestations of tuberculosis to be increased under unhealthy conditions [12]. Unfavourable environment and disadvantaged status also move the peak incidence of TL towards childhood.

Coexistence of an immunosuppressive condition significantly increases all extrapulmonary manifestations as well as TL. In a study in Brazil, Teresa Gomes found EPTB cases to be nearly doubled when compared to the cases without comorbidities [14]. A meta-analysis performed by Naing C et al. demonstrated the significant association between HIV and EPTB. HIV-related immunosuppression not only affects the clinical presentation of TB but also increases the frequency of EPTB as well [26]. Fifty-three to sixty-three percent of HIV-infected patients tend to have isolated EPTB [1].

5.2 Pathogenesis

Mycobacterium tuberculosis targets mainly the lungs, but dissemination to other organ is not rare. Lymphatic tissue is the most frequent extrapulmonary destination for mycobacterium. Bacilli infecting the lymph nodes may spread to the tissue via lymphatics or haematogenous dissemination from the primary source in the body, with contact with an open wound, or by alimentary tract.

Upon surpassing primary defence mechanisms of the upper respiratory tract and gaining access to the alveoli, the bacilli are engulfed by alveolar macrophages. Normally soon after phagocytosed by macrophages, many bacteria are exterminated inside the cell by fusion of lytic enzyme-filled lysosomes and phagosome. Mycobacterium tuberculosis, instead of extermination via fusion of phagosome and lysosome, outpasses this step with its various surface molecules interacting with the primary defence system and proliferates either in the phagosome or inside the cytoplasm until leaving the macrophage. Researches indicate that the cellular immune defence, antigen-specific T cell activation against tuberculosis, initiates soon after the bacteria reaches to the draining lymph node and dendritic cells play an important role in this dissemination [7, 11, 20, 44].

On the other hand, *Mycobacterium tuberculosis* is a slow-growing microorganism. Presentation of the bacteria to the draining lymph node by dendritic cells does not occur until the bacteria reaches to a sufficient amount to be recognized and presented. Later, upon presentation of the bacteria to the draining lymph nodes, effector T lymphocytes start to differentiate, and cellular defence takes place by migration of these effector T lymphocytes to the infected area. Thus, it is not surprising that the lymph nodes are the most common site of extrapulmonary tuberculous infection.

In addition, the affecting bacteria does not always reach to the lymph nodes after inhalation. Another mycobacterium species, *Mycobacterium bovis*, may be digested

orally and cause especially cervical and abdominal lymphadenitis. Cervical lymphadenitis due to *Mycobacterium bovis* represents a great vast of cases in countries where animals are infected with the bacteria and milk of these animals is consumed without pasteurisation.

5.3 Clinical Presentation

Depending on the subspecies of *Mycobacterium*, TL affects cervical-supraclavicular, mediastinal, axillary and inguinal lymph nodes with the order of frequency. The percentage of the involved cervical lymph nodes vary between percentages of 63% and 77% [13, 23]. Hence, clinical descriptions and symptomatology mostly described over cervical TL. Patients mostly complains of painless and slowly enlarging lymph nodes at the posterior cervical or supraclavicular region. Thus, patients show lymph node hyperplasia with unresponsiveness to antibiotics, especially from an endemic area, must be evaluated for TL.

Madegedara et al. with a study from an endemic area, Sri Lanka, analysed the frequency of affected lymph nodes in a group of 152 patients with isolated EPTB, and results are shown in the table below.

Site of aspiration	Percentage %
Cervical	78.94
Axillary	11.18
Cervical and axillary	3.28
Submandibular	3.28
Supraclavicular	1.31
Inguinal	1.31
Inguinal and axillary	0.66

Systemic symptomatology includes a low-grade fever, fatigue and weight loss. However, young children and immunocompromised HIV-positive patients may develop significant fever and rapidly enlarging lymph nodes [4].

Hyperplasia is the first reaction of the infected lymphatic tissue and occurs within weeks or months of duration. Development of a granuloma takes place gradually. The lymph node is firm, mobile and discrete initially and in time attaches to the surrounding tissue. Drainage from the swollen lymphatic tissue may occur in around 10% of cases [18, 23]. Usually, more than one lymph node at the area are involved, but one of them is prominent among others and is enlarged asymmetrically. Necrotic caseation gradually occurs in the affected lymph node. Eventually, following necrosis, the affected lymph node comprises a liquid content and starts to fluctuate. Later on, the content of the lymph node may drain freely through a formed track. The drainage may persist for months.

The swollen lymph node may resist and form ‘cold abscess’ despite adequate medication. Coinfection with other bacteria causes peri-lymphadenitis and other signs of inflammation; fever, colour change and pain occur [38].

Patients having concomitant TL and pulmonary tuberculosis will complain of classical tuberculosis symptoms consisting of coughing up blood, chest pain, unintentional weight loss, fatigue, fever, night sweats and chills. Accompanying HIV and childhood also increase the presence of concomitant constitutional tuberculosis symptoms.

A retrospective study performed by Popescu et al. determined that not a single LN but a lymph node group is involved in almost all patients. Besides, in the same study, it is concluded that a single lymph node association is much more common than multiple lymph nodes to be affected. As far, multiple lymph node involvement, matting enlargement and caseating necrosis are the main clinical findings in TL.

As the cervical lymph nodes are the most common group to be affected by TL, observing the clinical changes of LN is easier. In order to suspect clinically from TL, a five-stage classification of TL by Jones and Campbell in 1962 will be helpful to recognise the disease.

(i) Stage 1, enlarged, firm, mobile, discrete nodes showing non-specific hyperplasia
(ii) Stage 2, large rubbery nodes fixed to surround tissue owing to periadenitis
(iii) Stage 3, central softening due to abscess formation
(iv) Stage 4, collar-stud abscess formation
(v) Stage 5, sinus tract formation

Clinically, it is easy to observe TL while located at anatomically visible locations, but suspicion of TL is more challenging while located at other lymph node groups. Clinical signs at these cases depend on the blockage of lymphatic drainage of the area and compression effect on the surrounding structures.

Mediastinal TL: A distressing cough and chest pain may be the leading symptom of the mediastinal disease. However, compression of the neighbouring tissue may also develop signs for lymphadenomegaly. Patients may have atelectasis or positional dyspnea due to compression of one of the lungs, dysphagia due to oesophagal compression [36, 45] or cardiac tamponade [29]. Oesophagal perforation and fistula formation between the oesophagus and trachea also have been reported [27].

Axillary TL: Without existing pulmonary tuberculosis, patients may develop painless, gradually enlarging axillary mass. Blockage of lymphatic drainage and swelling of the preceding tissue may present.

Peritoneal TL: Periportal, peripancreatic and mesenteric lymph nodes are frequently involved [34]. Baik SJ et al. reported a case of obstructive jaundice caused by pericholedocal tuberculous lymphadenitis [3].

5.4 Diagnosis

Being mostly localised in a visible area makes it easy for suspicion for tuberculosis. However, putting the right diagnosis is still challenging. At an endemic area for TB, patients with lymphadenitis should be carefully questioned for contact with TB positive individuals, previous TB history, living environment, constitutional symptoms, concomitant diseases especially HIV, duration of the swelling and the change in the character of the swelling in time. With the suspicion, laboratory confirmation is essential. However, none of the laboratory tests are hundred per cent certain to exclude the disease.

(a) Mantoux test (Tuberculin Skin Test): Mantoux test remains a valuable test in diagnosing tuberculous diseases especially latent tuberculosis cases. The initial step for the test is the intradermal injection of five tuberculin unit (TU) (0.1 mL) of purified protein derivative to an area of the forearm without hair and measuring the size of the induration 48–72 h later. The need for a second visit of the patient and the challenges of interpreting the results due to prior vaccination are negative aspects of the test. Although it has difficulties with the application, Lakhey M emphasized the value of Mantoux test with a study consisted of 122 TL cases, concluding that the combination of cytology, staining and Mantoux test enhances the diagnostic efficiency [21].

(b) Acid-fast staining, Erlich-Ziehl-Neelsen stain (EZN): While having a concomitant pulmonary active tuberculosis, there is more chance to identify the bacteria with the classical acid-fast staining (AFS) method. However, a high load of bacteria, approximately over 1000 per mL, is needed to successfully determine the bacteria. Although the bacterial load is important for a positive result for EZN staining, the overall sensitivity is reported as 71.4% for pulmonary specimens and 24% for extrapulmonary specimens [19]. Additionally, collections obtained from a draining fistula, or other clinical specimens from the LNs, are valuable for investigation, and a positive EZN result is highly specific for tuberculous infection but still has false-positive and false-negative results.

(c) Histopathology: Histopathologically investigation of the specimen from the affected LN gives highly specific results. Material from the affected lymph may be collected in several ways. First of all, fine needle aspiration (FNA) is less invasive and easier. Depending on the location of the affected LN, aspiration may be performed with a simple syringe or with the use of complex techniques such as bronchoscopy or gastroscopy. In some clinical circumstances such as a firm and solid mass which it is not possible to aspirate, an excisional biopsy was performed in order to fully take out the swollen LN. The specimens obtained by either method are valuable for EZN staining, bacterial culture, rapid tests and histopathological examination. Lymphoid infiltrate, noncaseating granulomas and caseification inside the granuloma with Langerhans giant cells are histological indicators for TL. Although FNA is less invasive than an excisional biopsy, various studies concluded that excisional biopsy has greater value to determine TL [22, 31, 35].

(d) Bacterial culture: Growth of the bacteria on culture media is the gold standard for the diagnosis of tuberculosis. However, the growth in the media is slow (usually requires 2–4 weeks), and a negative culture result does not exclude the disease. The specimens obtained from the affected LN, especially by excisional biopsy, have the highest diagnostic value. Sputum or blood cultures may also be helpful.

(e) Polymerase chain reaction (PCR): It is widely available in developed and developing countries. Aljaferi et al. published a study in 2004 which concluded that PCR is a faster and a reliable test in the immediate characterisation of *Mycobacterium tuberculosis* in 96.2% cases included in the study [2].

(f) Nucleic acid amplification tests (NAATs): There are commercially available NAATs; Amplified Mycobacterium tuberculosis direct test (MTD, Gen-Probe), Xpert MTB/RIF (often called GeneXpert)), pyrosequencing and homebrews.

  (i) Gen-Probe MTD test is the first NAAT announced and approved by FDA for AFB-positive patients. Later in 1999, Enhanced MTD (E-MTD) was approved also for AFB negative patients. The test principle is transcription-mediated amplification and targets ribosomal RNA of *Mycobacterium tuberculosis*. Its sensitivity is over 70% and significantly increases in AFB-positive cases. Specificity for the test is 98%.

  (ii) Xpert MTB/RIF was approved by FDA in 2013 for detection of *Mycobacterium tuberculosis* in all types of clinical specimens. The test has higher sensitivity in high-burden countries, and it also tests the rifampicin resistance. Chang et al. made a meta-analysis using drug susceptibility tests and cultures as the gold standard and published the sensitivity and specificity of the test as 95% and 98%, respectively [9]. Other advantages of the test are being automated cartridge-based, eliminated contamination and fast results. The results may be obtained in less than 2 h.

  (iii) Pyrosequencing (PSQ) is also another NAAT and often used to detect mutations responsible for drug resistance. PSQ can be used on specimens which are AFB positive and tests for rıfampin, INH and quinolone mutations.

  (iv) HAIN is a line probe assay which is not yet approved by the FDA but detects INH, rifampin and quinolone resistance.

(g) Imaging: Depending on the localisation of the affected LN, imaging techniques may alternate.

  (i) Chest X-ray is the first imaging technique for tuberculosis. It is easily accessible, cheap and successful in displaying the calcification; thus it still remains as one of the first-order studies for diagnosing pulmonary tuberculosis. But ultrasonography is more convenient in TL.

  (ii) Ultrasonography: because of being mostly localized at cervical lymph nodes, USG is beneficial for defining the amount of the lymph nodes involved, shape and boards, matting, measuring the size of the lymph nodes and exploring whether there is adjacent soft tissue oedema.

Surrounding soft tissue oedema, necrosis inside the lymph node, matting and posterior improvement are in favouring criteria for TL against metastatic lymph node enlargement [47]. Upon the development of necrosis, the homogenous structure of the lymph node changes, and the centre may be visualised as a heterogeneous area. Additionally USG maybe helpful with guiding FNA from the lymph node.

(iii) CT and MRI are valuable tests in diagnosing TL. The ability to show the anatomical structures and the relationship of the affected lymph nodes with the adjacent tissue with a 3D model and to demonstrate central necrosis as weakened signals on CT and hyperintense on T2 MR images are the favourable specifications for the methods ([39]). Besides, CT is the best choice for evaluating abdominal lymph node tuberculosis. But distinguishing the necrosis of TB and squamous cell ca is still difficult with these methods. Due to high radioactivity, CT will not be the first choice in demonstrating lymph node; besides, in order to visualise the calcified centre, IV contrast, which may be toxic to the patient, will be needed. Although it is expensive and not available in many facilities, MRI can replace CT under these conditions.

(iv) PET-CT is a method generally used for investigation of tumour metastasis. Expensive, time-consuming and hardly found in most facilities. The value of diagnostic studies for TL is still controversial. However, it may be beneficial in differentiating some patterns of pulmonary tuberculosis like pulmonary and lymphatic pattern (Soussan et al) [37]. Additionally, some researchers reported PET-CT to be useful for following the response to antituberculous therapy [40, 46].

(h) Laboratory

(i) ESR is usually elevated but is not specific for TL.

(ii) IFN-gamma release assays (IGRAs): *Mycobacterium tuberculosis* differs from most other environmental mycobacteria and attenuated *Mycobacterium tuberculosis* which is known as Bacillus Calmette Guerin (BCG) and used for vaccination worldwide against tuberculosis. The difference in the genome is called 'Region of Difference' (RD1). The RD1 area encodes for nine proteins. The main principle of the method is to determine the presence of RD1 in suspected patients. White blood cells of persons infected by *Mycobacterium tuberculosis* will release IFN gamma when mixed with antigens. The presence of RD1 clinically indicates *Mycobacterium tuberculosis* infection, and the test is negative in patients who are vaccinated with BCG and infected by environmental mycobacteria. The two IGRAs approved by FDA are QuantiFERON-TB Gold In-Tube (QFT-GIT) test and T-SPOT TB test (T-Spot).

1. QuantiFERON-TB Gold In-Tube: ESAT-6, CFP-10 and TB7.7 are the three synthetic peptides as *Mycobacterium tuberculosis* antigens and are in a single mixture. IFN-gamma concentration is measured by the test.

2. T-SPOT TB test: Two proteins, ESAT6 and CFP10 of RD1, are used to activate T cells of the patient. Effector T cells that recognise the two proteins start to release IFN gamma.

One-day result and no need for a second visit are advantages of the IGRAs. However the high cost and required complex technique make the test less advisable for low-income countries; thus WHO does not only recommend IGRAs to replace Mantoux test but also disadvise to use for the diagnosis of active TB in low-income countries. CDC recommends the use of the tests as an aid in diagnosing *M. tuberculosis* infection with special conditions as contacted persons, pregnant and healthcare workers' screening (CDC fact sheets).

5.5 Differential Diagnosis

Although a vast majority of lymph node enlargements especially in high-burden countries are etiologically TL, several other causes have to be kept in mind. As well as other infections of the lymph nodes (e.g. toxoplasmosis, bartonellosis, fungal infections, tularemia), primary lymph node malignancies (esp lymphoma) and metastases, autoimmune diseases, drug reactions and some other syndromes like sarcoidosis, cystic fibrosis and storage disorders must be kept in mind for differential diagnosis. A general diagnostic algorithm starting with a good history, well examination, FNA cytology and GeneXpert testing is advised to be followed for the distinction of TL.

5.6 Treatment

Determining the causative agent of lymphadenitis and drug resistance is crucial for the choice of treatment. IDSA recommendations for TL caused by mycobacteria with no drug resistance are 2 months of isoniazid, rifampin, pyrazinamide and ethambutol and isoniazid and rifampin for the following 4 months [6].

During the treatment, a paradoxical lymph node enlargement, new lymph node involvement and a new draining sinus may occur. Paradoxical reactions may take place in 20%, 23% of HIV seronegative patients [10, 16]. In HIV-positive patients, with the contribution of antiretroviral therapy, it is more complicated to define paradoxical reactions.

Surgery is the first choice for nontuberculous lymphadenitis with cure rates over 70% [28]. In addition, surgical excision may be performed in patients with paradoxical reactions during therapy, patients who are not compliant with therapy and patients who feel uncomfortable with the existing lymph node enlargement or draining lymph node. However, antibiotic treatment is recommended even surgery is performed.

5.7 Follow-Up

Positive treatment criteria are the clinical improvement in symptoms and reduction in the size of a lymph node. Additionally, if needed, GeneXpert MTB test is useful in following up the response for the treatment.

References

1. Aaron L. Tuberculosis in HIV-infected patients: a comprehensive review. CMI. 2004;10(5):388–98.
2. Aljaferi AS. Diagnosis of tuberculous lymphadenitis by FNAC, microbiological methods and PCR: a comparative study. Cytopathology. 2004;15(1):44–8.
3. Baik SJ. A case of obstructive jaundice caused by tuberculous lymphadenitis: A literature review. Clin Mol Hepatol. 2014;20(2):208–213.
4. Bem C. Human Immunodeficiency virus positive tuberculosis lymphadenitis in central africa: clinical presentation of 157 cases. Int J Tuberc Lung Dis. 1995;20:876–82.
5. Brown TG. The influence of social factors on the incidence of extra-pulmonary tuberculosis infection. J Hyg (Lond). 1947;45(2):239–50.
6. Tuberculosis- United States, 2016. MMWR 2017;66(11);289–294.
7. Chackerian A, Alt J, Perera T, Dascher C. SMB Dissemination of Mycobacterium tuberculosis is influenced by host factors and precedes the initiation of T-cell immunity. Infect Immun. 2002;70:4501–9.
8. Chandir S. Extrapulmonary tuberculosis: a retrospective review of 194 cases at a tertiary care hospital in Karachi, Pakistan. J Pak Med Assoc. 2010;60(2):105–9.
9. Chang K, et al. Rapid and effective diagnosis of tuberculosis and rifampin resistance with Xpert MTB/RIF assay: a meta-analysis. J Infect. 2012;64(6):580–8.
10. Cho OH, Park KH, Kim T, et al. Paradoxical responses in non-HIV-infected patients with peripheral lymph node tuberculosis. J Infect. 2009;59:56–61.
11. Demangel C, Bertolino P, Britton WJ. Autocrine IL-10 impairs dendritic cell(DC)-derived immune responses to mycobacterial infection by suppressing DC trafficking to draining lymph nodes and local IL-12 production. Eur J Immunol. 2002;32:994–1002.
12. European Centre for Disease Preventation and Cotrol Annual epidemiological report Reporting on 2011 surveillance data and 2012 epidemic intelligence data. 2013.
13. Geldmacher H. Assessment of lymph node tuberculosis in northern Germany: a clinical review. Chest. 2002;121(4):1177–82.
14. Gomes T. Epidemiology of extrapulmonary tuberculosis in Brazil: a hierarchical model. BMC Infect Dis. 2014;14:9.
15. Hatipoğlu N and Güvenç H. (2017). Chapter 4 Peripheral Tuberculous Lymphadenitis: Clinical Approach and Medico-Surgical Management.
16. Hawkey CR, Yap T, Pereira J, et al. Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis. Clin Infect Dis. 2005;40:1368–71.
17. Ilgazlı A. Extrapulmonary tuberculosis: clinical and epidemiologic spectrum of 636 cases. Arch Med Res. 2004;35(5):435–41.
18. Kanlıkama M. Management strategy of mycobacterial cervical lymphadenitis. J Laryngol Otol. 2000;114:274–8.
19. Karadağ A. Comparison of culture, real-time DNA amplification assay and erlich-ziehl-neelsen for detection of mycobacterium tuberculosis. Balkan Med J. 2013;30(1):13–5.

20. Khader S, Partida-Sanchez S, Bell G, Jelley-Gibbs D, Swain S, et al. Interleukin 12p40 is required for dendritic cell migration and T cell priming after Mycobacterium tuberculosis infection. J Exp Med. 2006;203:1805–15.
21. Lakhey M. Diagnosis of tubercular lymphadenopathy by fine needle aspiration cytology, acid-fast staining and Mantoux test. JNMA J Nepal Med Assoc. 2009;48(175):230–3.
22. Lee KC. Contemporary management of cervical tuberculosis. Laryngoscope. 1992;102(1): 60–4.
23. Mert A. Tuberculous lymphadenopathy in adults: a review of 35 cases. Acta Chir Belg. 2002;102(2):118–21.
24. Müller GP. The Treatment of Tuberculous Cervical Lymphadenitis. Annals of Surgery 1913;LVIII(4):433–450.
25. Muluye D. Prevalence of tuberculous lymphadenitis in Gondar University Hospital, Northwest Ethiopia. BMC Public Health. 2013;13:435.
26. Naing C. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung. 2013;191(1):27–34.
27. Okten I, Management of esophageal perforation. Surg Today. 2001;31(1):36–9.
28. Panesar J, Higgins K, Daya H, Forte V, Allen U. Nontuberculous mycobacterial cervical adenitis: a ten-year retrospective review. Laryngoscope. 2003;113:149–54.
29. Paredes C, Delcampo F, Zamarron C, et al. Cardiac tamponade due to tuberculous mediastinal lymphadenitis. Tubercle. 1990;71:219–20.
30. Perlman DC, D'Amico R, Salomon N. Mycobacterial diseases of the head and the neck. Curr Inf Dis Rep. 2001;3(3):233.
31. Polesky A. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. Medicine. 2005;84(6):350–62.
32. Raul M. Popescu Lymph Node Tuberculosis- an attempt of clinico-morphological study and review of the literature. Rom J Morphol Embryol. 2014;55:553–67.
33. Rodriguez et al. Enfermedades infecciosas y microbiologia clinica vol 29 num 7 agosto settembre. 2011;29:502–9.
34. Shafer RW. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. Medicine (Baltimore). 1991;70:384–97.
35. Singh KK. Comparison of in-house polymerase chain reaction with conventional techniques for the detection of Mycobacterium tuberculosis DNA in granulomatous lymphadenopathy. J Clin Pathol. 2000;53(5):355–61.
36. Singh B, Moodly M, Goga AD, Haffejee AA, et al. Dysphagia secondary to tuberculous lymphadenitis. S Afr J Surg. 1996;34:197–9.
37. Soussan M, Brillet PY, Mekinian A, Khafagy A, Nicolas P, Vessieres A, Brauner M. Patterns of pulmonary tuberculosis on FDG-PET/CT. Eur J Radiol. 2012;81:2872–6.
38. Spyridis P. Mycobacterial cervical Lymphadenitis in children: clinical and laboratory factors of importance for differential diagnosis. Scand J Infect Dis. 2001;33(5)
39. Tan CH, Kontoyiannis DP, Viswanathan C, Iyer RB. Tuberculosis: a benign impostor. Am J Roentengenol. 2010;194:555–61.
40. Tian G, Xiao Y, Chen B, Xia J, Guan H, Deng Q. FDG PET/CT for therapeutic response monitoring in multi-site non-respiratory tuberculosis. Acta Radiol. 2010;51:1002–6.
41. Centers for Disease Control and Preventation, Treatment of tuberculosis, MMWR Recomm Rep. 2003;52:1–77.
42. William C. VORSANGER. Tuberculous Cervical Lymphadenitis. Cal West Med. 1937;47(3):194–198.
43. World Health Organisation. Global Tuberculosis Report 2017.
44. Wolf A, Desvignes L, Linas B, Banaiee N, Tamura T, et al. Initiation of the adaptive immune response to Mycobacterium tuberculosis depends on antigen production in the local lymph node, not the lungs. J Exp Med. 2008;205:105–15.
45. Xiong L, et al. Posterior mediastinal lymphadenitis with dysphagia as the main symptom a case report and literature review. J Thorac Dis. 2013;5(5):E189–94.

46. Yadla M, Sivakumar V, Kalawat T. Assessment of early response to treatment in extrapulmonary tuberculosis: role of FDG-PET. Indian J Nucl Med. 2012;27:136–7.
47. Ying M, Ahuja AT, Evans R, King W, Metreweli C. Cervical lymphadenopathy: sonographic differentiation between tuberculous nodes and nodal metastases from non–head and neck carcinomas. J Clin Ultrasound. 1998;26:383–9.
48. Forssbohm M, Zwahlen M, Loddenkemper R, Rieder HL. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. European Respiratory Journal. 2008;31(1):99–105.
49. Chan-Young. Extra-pulmonary and pulmonary tuberculosis in Hong Kong. Int J Tuberc Lung Dis. 2002;6(10):879–86.
50. CDC. Trends in Tuberculosis—United States, 2008, MMWR March 20, 2009 / 58(10);249–253.