ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Lymph Node Tuberculosis

Dipti Gothi[1]*, Anand Jaswal[2] and Sonam Spalgais[1]

[1]Pulmonary Medicine, ESI-PGIMSR Delhi, India

[2]Director Pulmonary Medicine, Medanta Medicity Gurgaon, India

***Corresponding Author**: Dipti Gothi, Pulmonary Medicine, ESI-PGIMSR, Delhi, India.

Received: October 31, 2016; **Published:** December 06, 2016

Abstract

Lymph node tuberculosis (LNTB) is one of the commonest forms extrapulmonary tuberculosis. Though, the diagnosis is relatively easy because of accessibility, there are wide a wide differential diagnoses, which can mimic tuberculosis, that sometimes culture is required to diagnose tuberculous lymphadenitis. Amongst the older diagnostic tools mantoux test is a very important investigation for the diagnosis of LNTB. Availability of molecular technology has further improved the ease of diagnosis. Molecular techniques are also useful for the early detection of drug resistance. The diagnosis of mediastinal has also improved in the last decade due to advent of endobronchial ultrasound. The treatment is similar to pulmonary tuberculosis. However, paradoxical reaction, which is observed, in 10-15% of immune-competent and about 50% of human immunodeficiency virus positive patients needs a special mention for an appropriate management of LNTB.

Keywords: *Tuberculosis; Lymph Node; Extrapulmonary; Antitubercular Therapy*

Introduction

Tuberculosis (TB) has been a major cause of suffering and death since times immemorial [1]. India, China, Indonesia, South Africa and Nigeria from rank first to fifth respectively in terms of absolute number of cases [2]. Tuberculosis is primarily considered to be a pulmonary disease [3]. Hence, the term "extrapulmonary TB" has been used to describe the occurrence of TB at body sites other than the lung. Lymph node (LN) is one of the commonest, easily diagnosable, easily treatable and least complicated forms of extrapulmonary tuberculosis [1]. The field of molecular diagnosis has improved our understanding of different strains of tuberculosis and enhanced the diagnosis of LN TB [4]. Recent years have witnessed a dramatic upsurge in cases of drug-resistant *Mycobacterium (M.) tuberculosis*, molecular diagnosis has been useful in that as well [1]. Knowledge about differential diagnosis and paradoxical reaction are essential tools for the management of LN TB. Short-course chemotherapy is the standard of care for this form of extrapulmonary TB, which is usually paucibacillary.

History

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 Latin for "glandular swelling." The disease was also 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 [1,5].

Epidemiology

Extrapulmonary tuberculosis comprises 10 - 50% of all tuberculosis in HIV negative patients and about 35-80%in HIV infected patients. TB lymphadenitis is seen in nearly 40 per cent of extrapulmonary TB [6-12] which constitutes about 15 to 20 per cent of all cases of TB in India. Overall amongst cases of LN TB, in HIV positive as well as negative patients, the commonest nodes to be involved are cervical lymph nodes, followed by the mediastinal and axillary nodes [13,14]. Cervical and mediastinal group of lymph nodes [8] are involved in 70% of cases [7].

Pathogenesis

Clinicopathologically tuberculous lymphadenitis cannot be distinguished from lymphadenitis due to non-tuberculous mycobacteria. Though, the pathogenesis and management remain diverse, it is important to know the pathogenesis of both for an appropriate management of tuberculous lymphadenitis. Tuberculous lymphadenitis is considered to be a local manifestation of the systemic disease, whereas lymphadenitis due to nontuberculous mycobacteria is truly a localized disease [6].

TB lymphadenitis

TBLN may occur due to 1) Reactivation of healed focus involved during primary infection 2) Progressive primary tuberculosis i.e. spread from lung into mediastinal lymph node 3) Spread from tonsil and 4) Hematogenous spread due to miliary TB. The commonest mode of development of tuberculous lymphadenitis is reactivation of healed focus and progressive primary tuberculosis. Both these modes of spread are due to systemic dissemination of *M. tuberculosis* [15]. *M. tuberculosis* usually enters the human body via the respiratory tract and forms primary complex or Ghon's complex in the posterior segment of upper lobe. The organisms within the Ghon's focus gain an access to the blood stream and may disseminate to extra thoracic organs. Usually the host defense curtails the organisms both at primary site and the extrapulmonary sites. The bacteria remain dormant but may serve as nidus for reactivation. Lymph node tuberculosis may also occur at the time of initial infection (progressive primary disease). Rarely, LN involvement may occur via spread from tonsils and adenoids [16,17] providing an early portal of entry or via haematogenous spread of TB bacilli as seen in miliary TB.

Lymphadenitis due to non-tuberculous mycobacteria (NTM)

NTM known to cause lymphadenitis are *M. scrofulaceum, M. avium-intracellulare* complex, and *M.kansaii*. Unlike tuberculous lymphadenitis, NTM lymphadenitis appears to be a truly localized disease. The pathogens usually enter the lymph nodes directly via oropharyngeal mucosa, salivary glands, tonsils, gingiva or conjunctiva. It is particularly an important mode of entry in children because deciduous teeth harbor NTM. NTM may reach lymph nodes in the neck via lymphatics leading to non-tuberculous involvement of lymph node, which is difficult to differentiate from tuberculous lymphadenitis [1,18].

Clinical Features

Tuberculous lymphadenitis most frequently involves the cervical lymph nodes (Figure 1) followed in frequency by mediastinal, axillary, mesenteric, hepatic portal, perihepatic and inguinal lymph nodes [4,13, 19]. It may present as a unilateral single or multiple painless slow growing mass or masses developing over weeks to months, mostly located in the posterior cervical and less commonly in supraclavicular region [20]. Classically patients present with low grade fever, weight loss and fatigue and somewhat less frequently with night sweats [21,22] Cough is not a prominent feature of tuberculous lymphadenitis [21]. Upto 57% of patients have no systemic symptoms [21,23]. Sinus formation is seen in nearly 10% of the mycobacterial cervical lymphadenitis (Figure 2) [18,24].

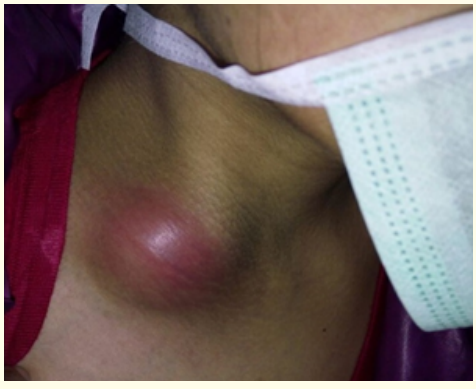


Figure 1: *Cervical lymph node with abscess formation.*

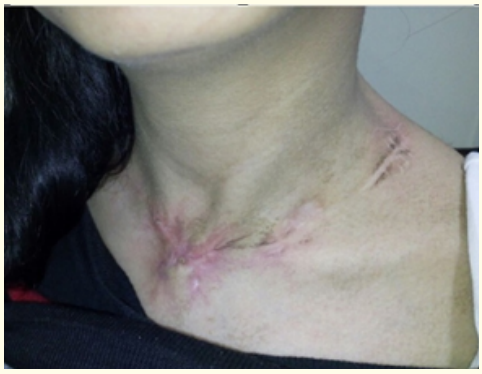


Figure 2: *Multiple scar formation, a complication of cervical lymph node tuberculosis.*

Jones and Campbell in 1962 described stages of TB LN. These are as follows: [25]

1. Enlarged, firm, mobile, discrete nodes
2. Large rubbery nodes fixed to surrounding tissue
3. Central softening-abscess
4. Collar stud formation
5. Sinus tract formation

Human Immunodeficiency Virus and tuberculous lymphadenitis

Tuberculous lymphadenitis is the most common form of extrapulmonary tuberculosis in HIV positive patients [26]. These patients are often older and males with involvement of multiple sites. Tender lymphadenopathy, fever, weight loss and co-existing pulmonary tuberculosis are more common in HIV seropositive patients as compared to HIV seronegatives [27].

Differential Diagnosis

Tuberculous lymphadenitis needs to be differentiated from lymphadenopathy due to other causes. These include granulomatous lymphadenopathy like non-tuberculous mycobacteria, sarcoidosis, lymphoma, berylliosis, tularemia lymphadenitis, cat scratch lymphadenitis, yersinia lymphadenitis, lymphogranuloma venereum, fungal infection, toxoplasma lymphadenitis (Piringer-Kuchinka lymphadenopathy), leprosy, syphilis and brucellosis [28-30]. In general, multiplicity, matting and caseation of the lymph nodes are features of tuberculous lymphadenitis but these are neither specific nor sensitive enough to be pathognomonic.

Diagnosis

The diagnostic modalities can be divided into 1) primary diagnostic studies and 2) ancillary diagnostic studies [30].

Primary diagnostic studies

Fine needle aspiration cytology (FNAC)

FNAC is safe, quick, easily available, relatively less invasive, practical and fairly reliable test for the diagnosis of peripheral LNTB [30]. It has emerged as a first-line diagnostic technique, especially in tuberculosis-endemic countries [30-32]. Caseating granuloma with acid-fast bacilli (AFB) positivity is fairly sensitive and specific for the diagnosis of TB. Although, caseating granuloma alone may not be very

specific because caseation can mimic necrosis and needs to be differentiated by special stains for collagen and reticulin [32]. Caseation has presence of reticulin whereas necrosis does not. This necrosis which can mimic 'caseation' along with granuloma can be seen in many diseases like lymphoma, sarcoidosis. Contrarily, positive AFB stain result has excellent specificity for *M. tuberculosis* in adults since AFB positivity can only be due to tuberculous or non-tuberculous mycobacteria. and non-tuberculous mycobacteria usually affects children [30]. Apart from Z-N stain, fluorescence microscopy using light-emitting diodes can also be used as inexpensive yet robust method of AFB smear analysis of FNAC specimens [33]. Overall, the diagnostic accuracy of lymph node FNAC ranges from 71.3% to 97% [34-42]. Histologic features, such as nonspecific lymphoid infiltrates, noncaseating granulomas, or Langerhans giant cells in areas of extensive caseous necrosis, support a diagnosis of probable tuberculosis [30].

Lymph node biopsy

The open biopsies with tissue culture are accepted as the gold standard to diagnose TBLN [30,43]. However, excisional biopsy is the most invasive approach to diagnosis. It has the highest sensitivity and has been recommended in cases involving multiple nodes, when the diagnosis is doubtful on FNAC or when drug resistance is suspected [30,44]. The surgical biopsy specimen should be collected both in saline and formalin separately. If care is not taken to send the sample separately into saline, culture would be negative and sensitivity report will be missed. Complications of biopsy include postsurgical pain, wound infection, sinus formation, and scar [30].

Culture

Isolation of mycobacteria by culture still represents the cornerstone on which the definitive diagnosis is based. The culture can be performed with both FNA and biopsy material. It has been shown that when combined with microscopy and culture the diagnostic accuracy of FNAC improves significantly [45]. Although culture can be performed with aspirated specimen, the positive rates are at times significantly lower in aspirated specimen as compared to biopsy specimen (17% Vs 80% respectively in a study from Hongkong) [46]. Although, culture establishes the diagnosis most definitively, the time consumed to grow mycobacteria makes it unsuitable for routine use. Hence, a few modern rapid methods have been developed [1]. These include: microcolony detection on solid media, septic check AFB method, microscopic observation of broth culture, the BACTEC 460 radiometric system, BACTEC MGIT 960 system, MB/BacT system and ESP II culture system [1,47].

Molecular tests

Molecular diagnosis or nucleic acid amplification (NAA) to detect mycobacterial DNA instead of detection of mycobacteria by traditional microbiological methods holds a promise in the diagnosis of tuberculosis. This is because they have higher sensitivity, are quicker and allow identification of the species and drug resistance earlier compared to conventional methods [1]. They have been available for diagnosis of pulmonary tuberculosis since the 1990's. Gen-Probe test was the first NAA test to get US Food and Drug Administration (FDA) approval for detection of pulmonary TB. Many other tests have been subsequently approved. Early molecular methods were polymerase chain reaction (PCR) designed to detect the *M. tuberculosis* complex only. Subsequently, line probe assays (LPAs) have been developed which combine NAA with hybridization. These can even detect drug resistance [48]. Guidelines for the use of NAA tests for the diagnosis of TB were published in 1996 and updated in 2000 and 2009 [49], 50Since then, NAA testing has become a routine procedure in many settings. The role of molecular tests or NAA in the diagnosis of LNTB is being discussed under following subtitles:

1) Amplified molecular tests for detecting *M. tuberculosis* 2) Test for detecting drug resistance to *M. tuberculosis*

1)Amplified molecular tests for detecting *M. tuberculosis:* These are PCR based fast and useful techniques for the demonstration of mycobacterial DNA fragments in patients with clinically suspected mycobacterial lymphadenitis. The most common target used in PCR is IS6110. Although tissue PCR is a less time-consuming test (one week) compared to the culture technique (MGIT about three weeks), PCR cannot give information about susceptibility to antimicrobial agents [6]. A systematic review of NAA using PCR technique in tuberculous lymphadenitis revealed highly variable and inconsistent results (sensitivity, 2% - 100%; specificity, 28% – 100%), with more favorable performance from commercial assays and with sample sizes of more than 0.20 uL. The systemic review had included commercial PCR

probes (Roche Amplicor, Abbott LCx, Gen probe MTDT, BD Probe Tec) and in-house polymerase chain reaction tests and possibly because of in-house PCR the specificity was variable [49]. Overall, PCR with biopsy specimen have much higher sensitivity and specificity compared to FNAC [51]. Real-time PCR assay for detecting the 16S ribosomal RNA gene of M. tuberculosis also show results similar to non-real time PCR both with FNA and biopsy specimens. For biopsy specimens, the sensitivity of real-time PCR in one of the reported studies is 63.4%, and the specificity is 96.9%. For FNA specimens, the sensitivity was 17.1%, and the specificity was 100%in the same study [52]. If FNAC samples are processed by combining microbiological (rapid culture) and molecular technique (PCR), the sensitivity and specificity improves significantly and biopsy can be avoided for confirmatory diagnosis of TBLN [53].

2) Test for detecting drug resistance to *M. tuberculosis:* [54] Advances in molecular technique beyond PCR allow simultaneous detection of *M. tuberculosis* DNA and drug resistant gene. They can be performed on cultured TB isolates or directly on pretreated primary specimens. Some assays (Cepheid Xpert and INNOLIPA) have been designed to detect TB and resistance to rifampicin only, while others (GenoType MTBDR plus) are able to detect both isoniazid and rifampicin-resistance in primary specimens and cultures. Cepheid GeneXpert MTB/RIF assay (Cepheid Xpert; Cepheid Xpert Inc., Sunnyvale, CA, USA) has been developed using semi-quantitative nested real time-PCR technique with facility of automated sample processing, and real-time-based molecular beacon assay. The commercially available INNO-LiPA Rif. TB kit (INNOLIPA; Innogenetics, Zwijndrecht, Belgium) is also an LPA, which is able to identify the M. tuberculosis complex and simultaneously detect genetic mutations in the region of the rpoB gene associated with rifampicin resistance. The GenoType MTBDRplus is LPA and includes three steps: DNA extraction, multiplex PCR amplification, and reverse hybridisation.

The Cepheid GeneXpert®, INNO-LiPA Rif. TBand GenoType MTBDRplus system have all been approved for TB detection in sputum by regulatory agencies [55-57]. Though all have not been approved for use in extrapulmonary TB, in 2013 the World Health Organization (WHO) endorsed the use Cepheid GeneXpert® for diagnosis of extrapulmonary TB [58,59]. There are multiple studies to assess the utility. A meta-analysis of FNAC samples for Cepheid GeneXpert has shown a sensitivity of 50% to 100% with pooled sensitivity of 83.1% (95% CI 71.4 – 90.7%) and pooled specificity of 93.6% (95% CI 87.9 – 96.8%) [60]. The pooled sensitivity for INNOLIPA for extrapulmonary sample is somewhat lower at 63 - 68% [54]. For the GenoType MDRDRplus assay, only one study analysed the sensitivity of TB identification and found a sensitivity of 91% (n = 10) [61]. Thus, molecular diagnosis specially for Cepheid GeneXpert system shows reasonable sensitivity and specificity. If, due to feasibility, they cannot be used for rapid diagnosis of LNTB they can definitely be very useful for rapid diagnosis of drug resistant LNTB.

Ancillary Diagnostic Tests

Tuberculin skin test

Tuberculin skin test (Mantoux test) is useful to show delayed type hypersensitivity reactions against mycobacterial antigens. Positive reactions (>10-mm induration) can occur in M. tuberculosis infections. Intermediate reactions (5- to 9-mm induration) can occur after BCG vaccination, M. tuberculosis infection or NTM infections. Negative reactions (≤ 4-mm induration) represent a lack of tuberculin sensitization [23]. The sensitivity and specificity of tuberculin skin test are 86% and 67%, respectively [62]. Though, tuberculin test is not useful in distinguishing prior BCG or prior infections or latent infection versus active disease, it is useful as an ancillary diagnostic test. It helps in differentiating TBLN from sarcoidosis and lymphoma because of anergy. Since there are no specific features on FNAC to differentiate the two conditions from TB with certainty, except a positive culture of M. Tuberculosis, [63-65] tuberculin anergy is useful in distinguishing sarcoidosis and lymphoma from TB [63-66].

Interferon-gamma release assays (IGRAs)

The interferon-gamma release assays (IGRAs) available are TB Gold and TB Platinum. They are useful for diagnosing latent TB infection like tuberculin testing, but unlike tuberculin test they can also be used to distinguish latent infection from BCG vaccination and non-tuberculous mycobacteria [67,68]. However, they cannot be used for the diagnosis of active tuberculosis. The Indian government banned serological antibody tests in 2012, and both Standards for TB Care in India (STCI) and International Standards for TB Care (ISTC)discourage the use of IGRAs for the diagnosis of active TB [69,70].

Diagnosis of Mediastinal Lymphadenitis

Mediastinal lymphadenopathy commonly presents with fever and cough [9]. It may also present with one of the complications like compression one of the bronchus leading to atelectasis (Figure 3a, b & c), lung infection and bronchiectasis or thoracic duct leading to chylous effusion. Other intrathoracic complications include dysphagia, oesophago-mediastinal fistula, and tracheo-oesophageal fistula [9]. Lone mediastinal LN enlargement due to TB is a rare manifestation [71]. Hence accompanying manifestations like lung involvement are useful for diagnosis. Contrast-enhanced computed tomography (CT)is a viable non-invasive cost effective option for the diagnosis of tuberculous mediastinal LN. Peripheral enhancement (rim enhancement) or multilocular (a subtype of peripheral enhancement) appearance (Figure 4a, b & c) is useful in differentiating tuberculous mediastinal LN from other causes like lymphoma sarcoidosis [72- 74]. Homogeneous enhancement or absence of 'classical' finding needs further differentiation with positron emission tomography (PET) scan or endobronchial ultrasound (EBUS). Both PET scan and EBUS are not easily available and are expensive. Judicious application of PET is helpful for differentiating tuberculous LN from sarcoidosis in cases with homogenously enhancing lymph node for detecting unsuspected sites and identifying potential site for tissue biopsy [75]. In the present era of evidence-based medicine, EBUS is a very useful tool for an accurate diagnosis of tuberculous mediastinal LN [76,77]. In a study by Sun., *et al.* on EBUS-guided transbronchial needle aspiration (TBNA) for intrathoracic TB lymph node, the sensitivity was 85%, specificity was 100%, positive and negative predictive values was 100 and 75%, respectively with the accuracy of 90% [76]. In a multicenter study of 156 patients, by Navani., *et al.* EBUS-TBNA was diagnostic of TB in 146 patients (94%; 95% CI 88% to 97%) [78]. EBUS-TBNA has been shown to have high negative predictive value and avoids use of more invasive mediastinoscopy for the diagnosis of mediastinal LN [78].

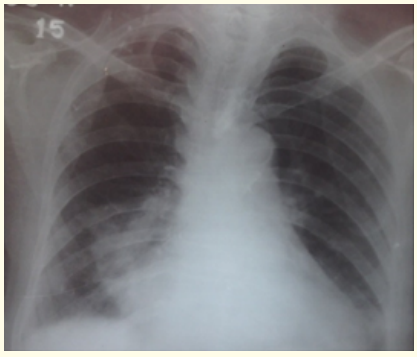


Figure 3a: *Chest radiograph showing collapse of right middle lobe.*

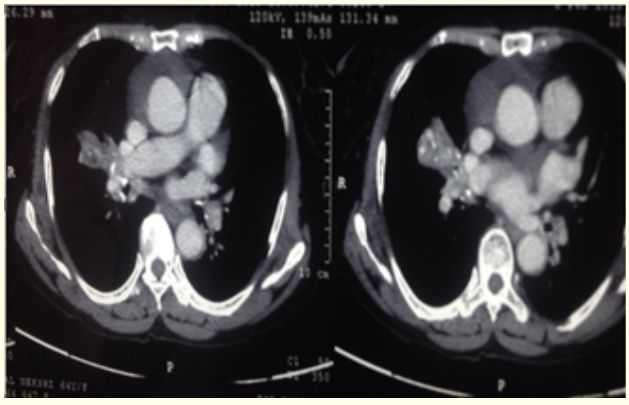


Figure 3b: *CT chest in mediastinal widow axial cut showing mediastinal lymph node with calcification causing obstruction of middle lobe bronchus.*

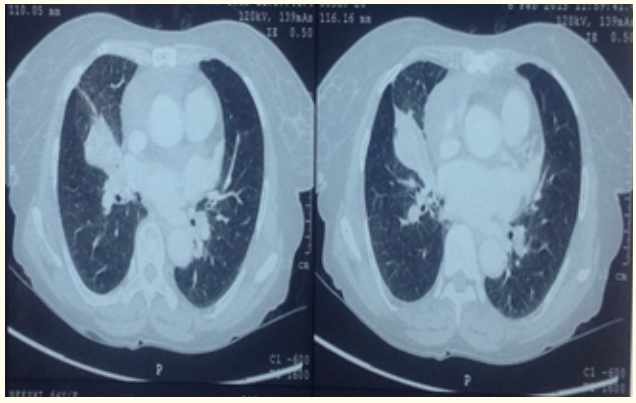


Figure 3c: *CT chest lung window showing collapse of right middle lobe (brock syndrome).*

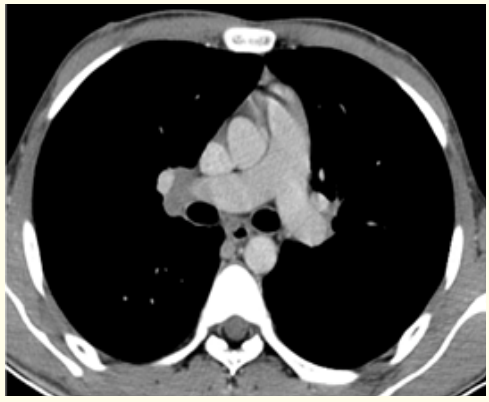
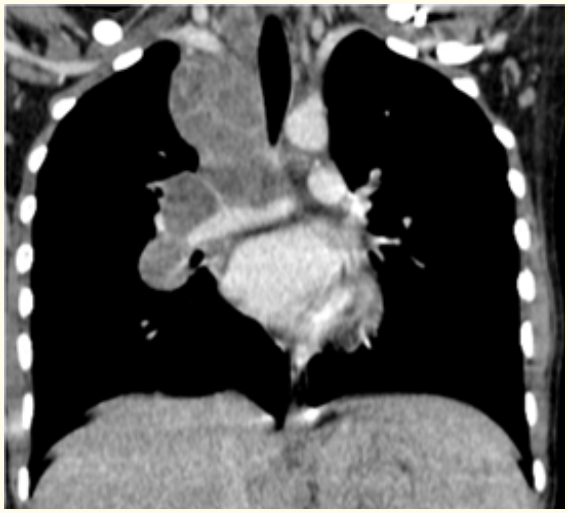


Figure 4a: *Axial CT thorax showing right hilar lymph node.*



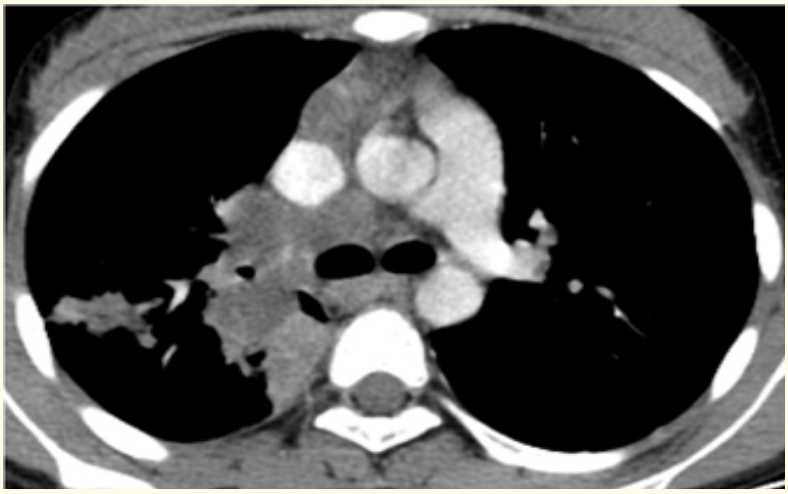


Figure 4b & c: *Coronal and Axial CECT showing bilateral hilar and mediastinal LN 'rim enhancement with central caseation' suggestive of tuberculosis.*

Treatment

The Infectious Disease Society of America (IDSA) and World Health Organization (WHO) recommend 6 months of treatment for drug-susceptible disease i.e. 2 months of isoniazid (H), rifampicin (R) pyrazinamide (Z) and ethambutol (E) in intensive phase followed by 4 months of rifampicin and isoniazid in continuation phase (2HRZE/ 2HR). In areas with high prevalence of isoniazid resistance WHO has recommended a regime of 2HRZE/4HRE [79,80]. The 6-month recommendation is supported by studies that showed no difference between 6 and 9 months of treatment in cure rates (89% – 94%) [81,82] or relapse rates (3%) [83]. HIV testing is recommended as part of the evaluation of all TB patients and patients in whom the disease is suspected. HIV testing is especially important in persons with EPTB because of the increased frequency of extrapulmonary involvement in persons with immunosuppression. Daily dosing is strongly recommended during the intensive phase for TB patients with known positive HIV status [80].

Paradoxical Reaction

A paradoxical reaction (PR) in a patient infected with tuberculosis is defined as the clinical (Figure 5) and/or radiological worsening (Figure 6a, b, c) of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves with anti-tuberculosis therapy [84]. Most reported cases are of tuberculosis lymph node or central nervous system [85]. It occurs in about 10 - 15% of immune-competent [85] and 22% to 60% with HIV-positive patients treated for tuberculous lyphadenitis [86,87]. The median time to development of a PR in HIV-negative patients is 60 days (14 to 270 days) [88]. In HIV, positive patients 90% of cases occur within 3 months after starting antiretroviral therapy(ART) [89].

The exact mechanism of PR remains uncertain. Immuno-reconstitution phenomenon has been suggested as a possible explanation. In HIV, positive patients, a paradoxical response may occur during reversal of the immunosuppressive state when highly active antiretroviral therapy (HAART) is co-administered within 2 months of anti-tuberculosis treatment. This phenomenon appears more frequently in those patients with a significant reduction in HIV viral load and an increase in CD4-lymphocyte count after HAART [90]. Management primarily consists of differentiating PR from treatment failure, drug resistance or another infection. Fine needle aspiration culture or biopsy culture is useful in differentiating paradoxical reaction from drug resistance if definitive diagnosis was made at the time of initial evaluation. The use of aspiration has been reported to be a successful therapeutic intervention for suppurative tuberculous lymphadenitis. 91Otherwise, reassurance is the single most important intervention required for the management of PR. Steroids have been considered as a means to

reduce the robust immune response in PR in general, but their use is controversial in LNTB [77]. Some authors report benefit [92,93]. but retrospective studies have shown that steroids do not prevent PR if steroids have been given since the beginning of treatment [94]. Also, steroid do not have any effect on the duration of PR [95,96].

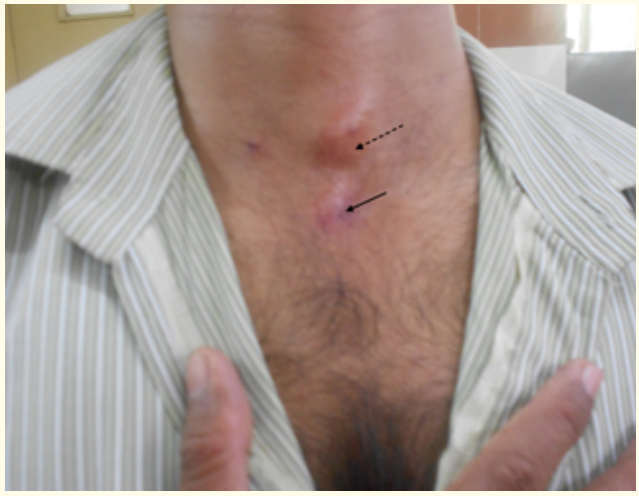


Figure 5: *A 36-year-old man with paradoxical reaction. The solid arrow shows suprasternal lymph node for which he was started on anti-tuberculosis treatment based on cytology showing AFB. 2 month later another lymph node shown by dotted arrow appeared. The culture for AFB was negative confirming paradoxical reaction.*

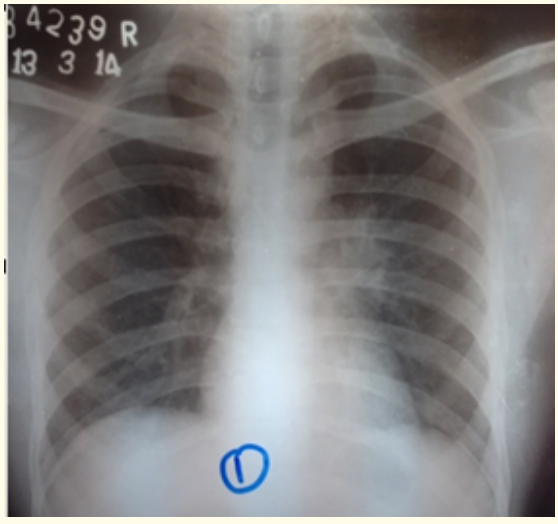


Figure 6a: *Chest radiograph showing left hilar and paratracheal lymph adenopathy in a patient with cervical lymph node. The diagnosis of tuberculosis was proven on cervical lymph node FNAC.*

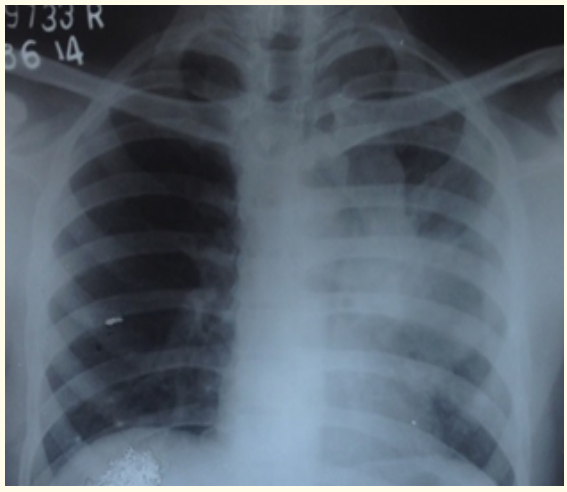


Figure 6b: *2 months after starting treatment, the patient had clinically improved but the chest radiograph showed paradoxical worsening. The chest radiograph shows collapse of left upper lobe due to enlargement of left hilar lymph node. The sputum and lymph node AFB culture was negative.*

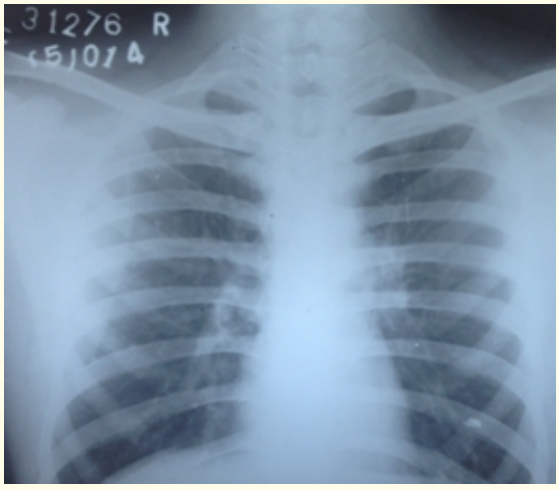


Figure 6c: *The chest radiograph on completion of treatment. It shows significant regression of hilar enlargement compared to figure 6a when the treatment was initiated.*

Non-tuberculous Lymph node tuberculosis

The most important alternative diagnosis of tuberculous lymphadenitis is non-tuberculous lymphadenitis (NTM) [97]. If culture is not performed on lymph node it is not possible to diagnose non-tuberculous LN. The presumptive diagnosis of NTM lymphadenitis is based on the histopathologic appearance of the lymph node showing caseating granulomata with or without AFB and, in the majority of cases, a negative tuberculin skin test. In the United States, only about 10% of the culture-proven mycobacterial cervical lymphadenitis in children has been reported to be due to *M. tuberculosis* [98]. In contrast, in adults, more than 90% of the culture-proven mycobacterial lymphadenitis is due to *M. tuberculosis* [99]. There are no formal studies done on prevalence of NTM from India. In absence of formal studies, it

is important to note that patients with non-resolving, suspected resistant lymphadenitis, diagnosis of NTM should be considered. The guiding principle for most localized NTM lymphadenitis that occurs in immunocompetent patients, due to any NTM species, is complete surgical excision of the involved lymph nodes [97].

Surgical Management

The indications for surgical management of TB lymphadenitis are [30]:

- Treatment failure: Surgical treatment is beneficial to establish the diagnosis and management of drug-resistant organisms.
- Adjuvant treatment for drug sensitive cases: For patients who have discomfort from tense, fluctuant lymph nodes surgical treatment is beneficial.
- Paradoxical reaction: In a retrospective review, aspiration, incision, and drainage or excision were associated with a trend toward a shorter duration of PR [96].
- Nontuberculous mycobacteria: In children with NTM lymph node removal has been associated with better outcomes.

Problems in the management of TB lymphadenitis

1. Appearance of new nodes/enlargement of existing nodes: [26] Appearance of new nodes is due to paradoxical reaction, drug resistance, erroneous diagnosis or disease caused by NTM. Most nodes that enlarge during therapy are due to PR. These ultimately respond to treatment. However, it is important to assess the patients for drug resistance if the history of irregularity in treatment is suspected or assess for revision of diagnosis if microbiological diagnosis was not performed during initial evaluation. Biopsy of lymph node with molecular/microbiological investigation may be required for the final confirmation.
2. Development of fluctuation: Appearance of fluctuation in one or more lymph nodes calls for aspiration under all aseptic precautions [26].
3. Appearance of sinus tracts: Any worsening after 8 weeks of therapy calls for en block resection of the involved lymph node chain to avoid appearance of ugly sinus tracts [26].
4. Residual lymph nodes after completion of treatment: At the end of therapy, about 10% of cases may be left with residual nodes [100]. Biopsy from these residual nodes often show caseating granuloma but culture would be negative. Presence of residual LN after ATT does not merit continuation of treatment unless the microbiological evidence (culture) support persistence of viable organisms.
5. Relapse: Relapse rates of up to 3.5% have been reported in patients treated for TB lymphadenitis [84]. This should be treated with the same drugs but culture or molecular diagnostic test must be performed to rule out resistance or NTM disease.
6. Drug resistance: Though it is at times difficult to confirm drug-resistance in LNTB, it is essential to demonstrate drug resistance prior to starting multi drug resistant regime. Similarly, single agent (Fluoroquinolones or others) should never be introduced even if response to treatment is not appropriate. Each case should be reasonably investigated with culture or molecular diagnostic tools. Also, appropriate measures should be taken to prevent the use of second line drugs in unproven cases.

Clinical Pearls

1. Lymph node enlargement due to tuberculosis is frequently seen in young population.
2. One must look for various other foci in the body. E.g. in a patient with cervical lymphadenopathy, chest radiograph and ultrasound abdomen/pelvis are important for providing information regarding not only the other disease sites but also follow up of treatment.

3. Microbiological and molecular test provide diagnostic certainty and confidence of response if sensitive strain is identified.

4. If abscess formation occurs it should be either aspirated to dryness (each time it recurs) or excised surgically. Otherwise scar and sinus often cause cosmetic disfigurement. Steroid should not be used if abscess formation has occurred.

5. As a personal observation of authors if multifocal paradoxical responses occurs without demonstration of drug resistance injection of streptomycin at the site of lymph node is useful.

6. For mediastinal lymph node CT scan, should not be used as routine follow up tool. CT scan should be reserved for initial and final assessment, as radiation exposure risk is significant. Chest radiograph remains a useful tool. A good MRI may also help in a particular case especially if abdominal gland has been involved.

Conclusion

LN TB, which is the commonest forms of extrapulmonary TB, is different from pulmonary tuberculosis in terms of diagnosis and management. Availability of molecular diagnosis and EBUS has changed the diagnostic scenario in the last decade though treatment has not changed much since the last decade.

Acknowledgements: Nil.

Conflict of Interest: Nil.

Bibliography

1. Handa U., *et al.* "Nodal tuberculosis revisited: a review". *Journal of Infection in Developing Countries* 6.1 (2012): 6-12.

2. "Global tuberculosis control: surveillance, planning, financing: WHO report" (2008).

3. Beyene D., *et al.* "Identification and genotyping of the etiological agent of tuberculous lymphadenitis in Ethiopia". *Journal of Infection in Developing Countries* 3.6 (2009): 412-419.

4. Mathema B., *et al.* "Molecular epidemiology of tuberculosis: current insights". *Clinical Microbiology Reviews* 19.4 (2006): 658-685.

5. Artenstein AW., *et al.* "Isolated peripheral tuberculous lymphadenitis in adults: current clinical and diagnostic issues". *Clinical Infectious Diseases* 20.4 (1995): 876-882.

6. Peto HM., *et al.* "Epidemiology of extrapulmonary tuberculosis in the United States, 1993-2006". *Clinical Infectious Diseases* 49.9 (2009): 1350-1357.

7. Dandupat MC., *et al.* "Peripheral lymph node tuberculosis: a review of 80 cases". *British Journal of Surgery* 77.8 (1990): 911-912.

8. Gothi D and Joshi JM. "Clinical and laboratory observations of tuberculosis at a Mumbai (India) clinic". *Postgraduate Medical Journal* 80.940 (2004): 97-100.

9. Sharma SK and Mohan A. "Extrapulmonary tuberculosis". *Indian Journal of Medical Research* 120 (2004): 316-353.

10. Aaron L., *et al*. "Tuberculosis in HIV-infected patients: a comprehensive review". *Clinical Microbiology and Infection* 10.5 (2004): 388-398.

11. Aguado JM and Castrillo JM. "Lymphadenitis as a characteristic manifestation of disseminated tuberculosis in intravenous drug abusers infected with human immunodeficiency virus". *Journal of Infection* 14.2 (1987): 191-193.

12. Finfer M., *et al.* "Fine needle aspiration biopsy diagnosis of tuberculous lymphadenitis in patients with and without the acquired immune deficiency syndrome". *Acta Cytologica* 35.3 (1991): 325-332.

13. Thompson MM., *et al.* "Peripheral tuberculous lymphadenopathy: a review of 67 cases". *British Journal of Surgery* 79.8 (1992): 763-764.

14. Geldmacher H., *et al*. "Assessment of lymph node tuberculosis in northern Germany: a clinical review". *Chest* 121.4 (2002): 1177-1182.

15. Kent DC. "Tuberculous lymphadenitis: not a localized disease process". *American Journal of the Medical Sciences* 254.6 (1967): 866-874.

16. Chavollo R., *et al*. "Primary Tuberculosis of Tonsil" *International Journal of Pediatric Otorhinolaryngology* 1.2 (2006): 150-153.

17. Belizna C., *et al.* "Tonsillar and lymph node tuberculosis revealing asymptomatic pulmonary tuberculosis". *Q J Med* 100.2 (2007): 800-801.

18. Kanlikama M., *et al.* "Management strategy of mycobacterial cervical lymphadenitis". *Journal of Laryngology & Otology* 114.4 (2000): 274-278.

19. Brizi MG., *et al.* "Diagnostic imaging of abdominal tuberculosis: gastrointestinal tract, peritoneum, lymph nodes". *Rays* 23.1 (1998): 115-125.

20. Penfold CN and Revington PJ. "A review of 23 patients with tuberculosis of the head and neck". *British Journal of Oral and Maxillofacial Surgery* 34.6 (1996): 508-510.

21. Kvaerner KJ., *et al.* "Surgery required to verify atypical mycobacterial infections". *International Journal of Pediatric Otorhinolaryngology* 61.2 (2001): 121-128.

22. Lee KC., *et al.* "Contemporary management of cervical tuberculosis". *Laryngoscope* 102.1 (1992): 60-64.

23. Mohapatra PR and Janmeja AK. "Tuberculous Lymphadenitis". *Journal of the Association of Physicians of India* 57 (2009): 585-590.

24. Konishi K., *et al.* "Study of tuberculosis in the field of otorhinolaryngology in the past 10 years". *Acta Otolaryngology Supple* 535 (1998): 244-249.

25. Jones PG and Campbell PE. "Tuberculous lymphadenitis in childhood: the significance of anonymous mycobacteria". *British Journal of Surgery* 50 (1962): 302-314.

26. Gupta PR. "Difficulties in managing lymph node tuberculosis" *Lung India* 21.4 (2004): 50-53.

27. Bem C. "Human immunodeficiency virus positive tuberculosis lymphadenitis in Central Africa: clinical presentation of 157 cases". *International Journal of Tuberculosis and Lung Disease* 1.3 (1997): 215-219.

28. Asano S. "Granulomatous Lymphadenitis". *Journal of Clinical and Experimental Hematopathology pathology* 52.1 (2012): 1-16.

29. Al-MaghrabiJA., *et al.* "Hodgkin's lymphoma with exuberant granulomatous reaction". *Saudi Medical Journal* 27.12 (2006): 1905-1907.

30. Fontanilla J., *et al.* "Current Diagnosis and Management of Peripheral Tuberculous Lymphadenitis". *Clinical Infectious Diseases* 53.6 (2011): 555-562.

31. Ellison E., *et al.* "Fine needle aspiration diagnosis of mycobacterial lymphadenitis. Sensitivity and predictive value in the United States". *Acta Cytologica* 43.2 (1999): 153-157.

32. Wright CA., *et al.* "Diagnosing mycobacterial lymphadenitis in children using fine needle aspiration biopsy: cytomorphology, ZN staining and autofluorescence-making more of less". *Diagnostic Cytopathology* 36.4 (2008): 245-251.

33. vanWyk AC., *et al.* "The use of light-emitting diode fluorescence to diagnose mycobacterial lymphadenitis in fine- needle aspirates from children from children". *International Journal of Tuberculosis and Lung Disease* 15.1 (2011): 56-60.

34. Goel MM., *et al.* "Polymerase chain reaction vs. conventional diagnosis in fine needle aspirates of tuberculous lymph nodes". *Acta Cytologica* 45.3 (2001): 333-340.

35. Chao SS., *et al.* "Tuberculous and nontuberculous cervical lymphadenitis: a clinical review". *Otolaryngology Head and Neck Surgery* 126.2 (2002): 176-179.

36. Gupta AK., *et al.* "Reliability and limitations of fine needle aspiration cytology of lymphadenopathies. An analysis of 1,261 cases". *Acta Cytologica* 35.6 (1991): 777-783.

37. Gupta AK., *et al.* "Critical appraisal of fine needle aspiration cytology in tuberculous lymphadenitis". *Acta Cytologica* 36.3 (1992): 391-394.

38. Das DK., *et al.* "Tuberculous lymphadenitis: correlation of cellular components and necrosis in lymph- node aspirate with A.F.B. positivity and bacillary count". *Indian Journal of Pathology and Microbiology* 33.1 (1990): 1-10.

39. Kumar N., *et al.* "AFB staining in cytodiagnosis of tuberculosis without classical features: a comparison of Ziehl-Neelsen and fluorescent methods". *Cytopathology* 9.3 (1998): 208-214.

40. Pandit AA., *et al.* "Tuberculous lymphadenitis: extended cytomorphologic features". *Diagnostic Cytopathology* 12.1 (1995): 23-7.

41. Clarridge JE., *et al*. "Large-scale use of polymerase chain reaction for detection of Mycobacterium tuberculosis in a routine mycobacteriology laboratory". *Journal of Clinical Microbiology* 31.8 (1993): 2049-56.

42. Budhwar P., *et al*. "Immunocytochemistry versus nucleic acid amplification in fine needle aspirates and tissues of extrapulmonary tuberculosis". *Journal of Cytology* 29.3 (2012): 157-164.

43. Supiyaphun P., *et al*. "Diagnostic tests for tuberculous lymphadenitis: fine needle aspirations using tissue culture in mycobacteria growth indicator tube and tissue PCR". *Asian Biomedicine* 45 (2010): 787-792.

44. Blaikley JF., *et al*. "Management of peripheral lymph node tuberculosis in routine practice: an unselected 10-year cohort". *International Journal of Tuberculosis and Lung Disease* 15.3 (2011): 375–378.

45. Gadre DV., *et al*. "Diagnosis of Tubercular Cervical Lymphadenitis by FNAC, Microscopy and Culture". *Indian Journal of Tuberculosis* 38 (1991): 25.

46. Lau SK., *et al*. "Efficacy of fine needle aspiration cytology in the diagnosis of tuberculous cervical lymphadenopathy". *Journal of Laryngology & Otology* 104.1 (1990): 24–27.

47. "What is new in the diagnosis of tuberculosis? Part I: techniques for diagnosis of tuberculosis". Indian Council of Medical Research Bulletin 32.8 (2002).

48. Bateson A., *et al*. "Molecular Diagnosis of Active Pulmonary Tuberculosis". In:Tuberculosis: Laboratory Diagnosis and Treatment Strategies (Advances in Molecular and Cellular Microbiology) [Kindle Edition] Eds: McHugh TD, CABI Boston.

49. Daley P[1]., *et al*. "Nucleic acid amplification tests for the diagnosis of tuberculous lymphadenitis: a systematic review". *International Journal of Tuberculosis and Lung Disease* 11.11 (2007): 1166-76.

50. "Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis". MMWR January 16 58.01 (2009): 7-10.

51. Derese Y., *et al*. "Comparison of PCR with standard culture of fine needle aspiration samples in the diagnosis of tuberculosis lymphadenitis". *Journal of Infection in Developing Countries* 6.1 (2012): 53-57.

52. Linasmita P., *et al*. "Evaluation of Real-time Polymerase Chain Reaction for Detection of the 16S Ribosomal RNA Gene of Mycobacterium tuberculosis and the Diagnosis of Cervical Tuberculous Lymphadenitis in a Country With a High Tuberculosis Incidence". *Clinical Infectious Diseases* 55.3 (2012): 313-321.

53. Supiyaphuna P., *et al*. "Diagnostic tests for tuberculous lymphadenitis: fine needle aspirations using tissue culture in mycobacteria growth indicator tube and tissue PCR". *Asian Biomedicine* 4.5 (2010): 787-792.

54. "Technical Report ERLN-TB. Opinion On Rapid Molecular Assays For Diagnosis Of TB And Drug Resistance". *European Centre for Disease Prevention and Control* (2013).

55. "Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system". *Geneva, World Health Organization* (2011).

56. "FDA permits marketing of first U.S. test labeled for simultaneous detection of tuberculosis bacteria and resistance to the antibiotic rifampin". *US Food and Drug Administration* (2013).

57. Weyer K., *et al*. "Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF". *European Respiratory Journal* 42.1 (2013): 252-271.

58. "Policy update: Automated realtime nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children". World Health Organization (2013).

59. Pai M and Nathavitharana R. "Extrapulmonary Tuberculosis: New Diagnostics and New Policies". *Indian Journal of Chest Diseases & Allied Sciences* 56.2 (2014): 71-73.

60. Denkinger CM., *et al*. "Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: asystematic review and meta-analysis". *European Respiratory Journal* 44.2 (2014): 435-446.

61. Neonakis IK., *et al*. "Evaluation of GenoType mycobacteria direct assay in comparison with Gen-Probe Mycobacterium tuberculosis amplified direct test and GenoTypeMTBDRplus for direct detection of Mycobacterium tuberculosis complex in clinical samples". *Journal of Clinical Microbiology* 47.8 (2009): 2601-2603.

62. Song KH., *et al*. "Usefulness of the whole-blood interferon-gamma release assay for diagnosis of extrapulmonary tuberculosis". *Diagnostic Microbiology and Infectious Disease* 63.2 (2009): 182-187.

63. Zhao NA, Yang J and Zhang G. "Differential diagnosis between AML infiltration, lymphoma and tuberculosis in a patient presenting with fever and mediastinal lymphadenopathy: A case report". *Oncology Letters* 7.3 (2014): 705-708.

64. Babu K. "Sarcoidosis in tuberculosis-endemic regions: India". *Journal of Ophthalmic Inflammation and Infection* 3 (2013): 53.

65. Xiong L., *et al*. "Posterior mediastinal tuberculous lymphadenitis with dysphagia as the main symptom: a case report and literature review". *Journal of Thoracic Disease* 5.5 (2013): E189-E194.

66. Smith-Rohrberg D and Sharma SK. "Tuberculin skin test among pulmonary sarcoidosis patients with and without tuberculosis: its utility for the screening of the two conditions in tuberculosis-endemic regions". *Sarcoidosis vasculitis and diffuse lung disease* 23.2 (2006): 130-134.

67. Metcalfe JZ., *et al*. "Interferon-gamma release assays for active pulmonary tuberculosis diagnosis in adultsin low- and middle-income countries: systematic review andmeta-analysis". *Journal of Infectious Diseases* 204.Suppl 4 (2011): S1120-S1129.

68. Fan L., *et al*. "Interferongamma release assays for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis". *FEMS Immunology & Medical Microbiology* 65.3 (2012): 456-466.

69. "International Standards for Tuberculosis Care, 3rd edition". TB CARE I (2014).

70. "Standards for TB Care in India". World Health Organization (Country Office for India) (2015).

71. Kumar N., *et al*. "Isolated Mediastinal Tuberculosis: A Rare Entity". *Journal of the Association of Physicians of India* 61.3 (2013): 202-203.

72. Chen J., *et al*. "Differentiation of tuberculosis from lymphomas in neck lymph nodes with multidetector-row computed tomography". International Journal of Tuberculosis and Lung Disease 16.12: 1686-1691.

73. Eison M., *et al*. "A study of patients with isolated mediastinal and hilar lymphadenopathy undergoing EBUS-TBNA". *BMJ Open Respiratory Research* 1.1 (2014): e000040.

74. Jaiswal A., *et al*. "Computed Tomography Features Of Tuberculous Mediastinal Lymphadenopathy". Indian Journal of Tuberculosis 59 (1992): 229.

75. Wong ML. "PET/CT scans in sarcoidosis: a review". *South African Respiratory Journal* 20 (2014): 7-16.

76. Chhajed PN., *et al*. "Endobronchial ultrasound-guided transbronchial needle aspiration: The standard of care for evaluation of mediastinal and hilar lymphadenopathy". *Journal of Cancer Research and Therapeutics* 9.4 (2013): 549-551.

77. Sun J., *et al*. "Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculosis". *Annals of Thoracic Surgery* 96.6 (2013): 2021-2027.

78. Navani N., *et al*. "Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: A multicentre study". *Thorax* 66.10 (2011): 889-893.

79. "Treatment of tuberculosis". *Centers for Disease Control. Morbidity and Mortality Weekly Report Recommendations and Reports* 52 (2003): 1-77.

80. "Treatment of tuberculosis: guidelines – 4th ed". *World Health Organization* (2009).

81. Campbell IA., *et al*. "Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results". *Respiratory Medicine* 87.8 (1993): 621-623.

82. Yuen AP., *et al*. "Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy". *Otolaryngology–Head and Neck Surgery* 116.2 (1997): 189-192.

83. vanLoenhout-Rooyackers JH., *et al*. "Shortening the duration of treatment for cervical tuberculous lymphadenitis". *European Respiratory Journal* 15.1 (2000): 192-195.

84. Breen RAM., *et al*. "Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection". *Thorax* 59.8 (2004): 704-707.

85. Cheng VCC. "Paradoxical Response during Anti-tuberculosis Therapy". *Medical Bulletin* 11.1 (2006): 20-21.

86. Narita M., *et al*. "Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS". *American Journal of Respiratory and Critical Care Medicine* 158.1 (1998): 157-161.

87. Wendel KA., *et al*. "Paradoxical worsening of tuberculosis in HIV-infected persons". *Chest* 120.1 (2001): 193-194.

88. Cheng VC., *et al*. "Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients". *European Journal of Clinical Microbiology & Infectious Diseases* 21.11 (2002): 803-809.

89. Breton G., *et al*. "Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy". *Clinical Infectious Diseases* 39.11 (2004): 1709-1712.

90. Navas E., *et al.* "Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy". *Archives of Internal Medicine* 162.1 (2002): 97-99.

91. Meybeck A., *et al*. "Needle aspiration in paradoxical hypertrophy of tuberculous lymphadenitis [in French]". *Revue des Maladies Respiratoires* 20.6 (2003): 973-977.

92. Garcia Vidal C and Garau J. "Systemic steroid treatment of paradoxical upgrading reaction in patients with lymph node tuberculosis". *Clinical Infectious Diseases* 41.6 (2005): 915-917.

93. Park KH., *et al*. "Post-therapy paradoxical response in immunocompetent patients with lymph node tuberculosis". *Journal of Infection* 61.5 (2010): 430-434.

94. Afghani B and Lieberman JM. "Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review". *Clinical Infectious Diseases* 19.6 (1994): 1092-1099.

95. Cho OH., *et al*. "Paradoxical responses in non-HIVinfected patients with peripheral lymph node tuberculosis". *Journal of Infection* 59.1 (2009): 56-61.

96. Hawkey CR., *et al*. "Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis". *Clinical Infectious Diseases* 40.9 (2005): 1368-1371.

97. Griffith DE., *et al*. "An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases". *American Journal of Respiratory and Critical Care Medicine* 175.4 (2007): 367-416.

98. Wolinsky E. "Mycobacterial lymphadenitis in children: a prospective study of 105 nontuberculous cases with long-term follow-up". *Clinical Infectious Diseases* 20.4 (1995): 954-963.

99. Wallace RJ Jr., *et al*. "American Thoracic Society statement: diagnosis and treatment of disease caused by nontuberculous mycobacteria". *American Journal of Respiratory and Critical Care Medicine* 156 (1997): S1-S25.

100. Campbell IA. "The treatment of superficial tuberculous lymphadenitis". Tuberculosis 71.1 (1990): 1-3.

Volume 2 Issue 5 December 2016