General Surgery

KEYWORDS:
Extraperitoneal Tuberculosis, Diagnostic criteria, Macrophage, Immune response, surgical intervention.

# Extrapulmonary Tuberculosis: Are We Barking up the wrong tree?! A 4 year naturalistic follow up study

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**ABSTRACT**

**AIM:**
To determine if extra-pulmonary tuberculosis (EPTB) is a communicable disease as commonly perceived or a disease of host immune dysfunction.

**PATIENTS AND METHODS:**
Patients with clinical suspicion of EPTB, in general surgery and orthopaedic department of twin hospitals of Deccan College of Medical Sciences, between the period of january 2015 and december 2017, were investigated appropriately and those found to have confirmed TB were enrolled in the study and followed up for 1 year.

Simultaneously patient's details registered under RNTCP in the two local community health centres were collected and compared with the hospital based study.

**RESULTS:**
Of 319 patients with clinical features, 267 were confirmed with EPTB- maximum number with lymph nodal disease (127) followed by extremity bone and joint (63), spine (38), skin and soft tissues (25) and abdominal tb (19). Method of confirmation differed for each site. Detection by AFB being the least sensitive followed by AFB culture. The best method of diagnosis being histopathological examination.

**CONCLUSION:**
Immunity plays a major role in site of reactivation of TB and healing of disease irrespective of duration of anti-tuberculous chemotherapy or surgical intervention.

**INTRODUCTION:**
Tuberculosis has been a dreaded disease and is still considered to be responsible for causing major morbidity and mortality throughout the world, more so in the third world countries of Asia, Africa and Latin America.

The Lungs are supposedly the primary site of infection from where the organisms are transported to the draining lymph nodes and widely disseminated throughout the body [1]. EPTB may be associated with primary TB in the lungs or as is more often the case, without any evidence of primary lung pathology, where the primary lesion causes the same inflammatory response as in any bacterial pneumonia and heals without any sequelae [1,2].

Earlier and in third world countries like India, even in present times, the common perception is that Tuberculosis is a disease of only the pulmonary system[3,4]. The concept of EPTB is still novel in the population with most patients landing up with physicians or pulmonologists on being diagnosed with extrapulmonary TB or refusing to believe the diagnosis claiming they have no pulmonary symptoms.

Another common misconception is that EPTB is common only in severe immunosuppressed conditions like HIV, AIDS and organ transplantation patients. This is propagated by studies arising in the west mostly USA [5,6], which is taken and repeated in other studies from Asia and southeast Asia [7,8]. Only recently are studies being published which are showing gradual increase in proportion of patients with EPTB compared to pulmonary TB patients even in the normal population which is ironically being attributed to better surveillance, early detection and treatment of pulmonary TB[7,9].

Many of the studies on EPTB have taken detection of AFB on microscopy and AFB culture as the basis for inclusion in their studies [3,5,10] which is confounding considering the difficulty in isolating tubercle bacilli in tissues and body fluids [1,2].

Even the presence of tubercle bacilli detected by bacterial nucleic acid amplification (CBNAAT) is not confirmatory of the disease due to its extreme sensitivity to contamination in high endemic settings generating high false positive results as it is unable to differentiate between viable and dead AFB [11].

Most reliable method of diagnosis still being finding of 'Tubercle' on histopathological examination- a more or less discrete focus of granulomatous inflammation consisting of lymphocytes, epithelioid cells, macrophages and giant cells- characteristic features of tuberculous granulomas being a form of tissue necrosis known as caseation- so called because of its consistency of cheese[1].

Cytological examination of the specimens revealing the presence of epithelioid cells and langhans giant cells in a necrotic background

corresponding to caseous necrosis being equally confirmative [12].

## ETHODOLOGY:

The study was carried out in two levels- first, in hospitals attached to Deccan college of medical sciences in departments of General Surgery and Orthopedics and second was in community health centers serving the general population in areas surrounding the two teaching hospitals, who were implementing the RNTCP schemes and they had a record of patients with TB- both new as well as those on treatment. In the teaching hospitals based study, the above mentioned departments collected data according to the following proforma for 3 years from Jan 2015-Dec 2017 and the patients were followed up till Dec 2018.

## PROFORMA FOR COLLECTION OF DATA

| | | |
|---|---|---|
| IDENTIFICATION NUMBER | AGE | GENDER |
| 1. PRIMARY SITE AFFECTED | | |
| 2. H/O PULMONARY TB | YES/NO | |
| 3. H/O BCG IMMUNIZATION | YES/NO | |
| 4. H/O DIABETES MELLITUS | YES/NO | |
| 5. CHEST X-RAY (e/o pulmonary involvement) | PRESENT/ABSENT | |
| 6. DIAGNOSIS BASED ON<br>• RADIOLOGICAL<br>• PATHOLOGICAL | USG/CT/MRI<br>FNAC/HPE | |
| 7. CBNAAT (if done) | POSITIVE/NEGATIVE | |
| 8 AFB MICROSCOPY AND CULTURE (if done) | POSITIVE/NEGATIVE | |
| 9. TOTAL DURATION of ATT | | |
| 10. SURGICAL INTERVENTION (if done) | DIAGNOSTIC/THERAPEUTIC | |
| 11. TOTAL TIME FOR RESOLUTION OF SYMPTOMS/ HEALING | • After starting ATT:<br>• After surgical intervention (if any): | |
| 12. RECURRENCE | YES/NO<br>• Within 1 year of ATT completion<br>• Healing after surgical intervention | |

In the community health center based study, the total number of patients registered in the program from Jan 2015- Dec 2017 were taken and divided into two groups pulmonary and extrapulmonary – pleural disease being included into the extrapulmonary category. Sputum positivity, Chest X-ray, History of previous treatment of TB and Retroviral positivity was taken into account and compared between the two groups. Results were analysed and checked for statisitical significance by Chi Square test.

Method of detection and confirmation of EPTB in Appendix 1 and 2.

## RESULTS:

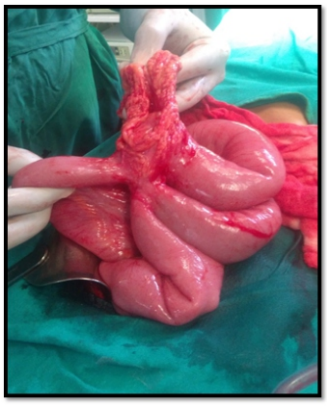
**Table 1: Patient Data**

| Site of TB | No. Enrolled | No. Confirmed | By Imaging | By Cytology | HPE | CBNAAT | | AFB Positive on microscopy | AFB |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Done | Positive | | Done |
| Lymph Nodes | 148 | 127 | - | 76 | 51 | 13 | 6 | 10 | 64 |
| Abdomen | 30 | 19 | - | 2 | 14 | 5 | 3 | 1 | 9 |
| Skin & Soft tissues | 25 | 20 | - | 3 | 17 | 3 | 3 | 4 | 12 |
| Spine | 44 | 38 | 13 | 7 | 18 | 6 | 4 | 5 | 26 |
| Other Skeletal Bone & Joint | 72 | 63 | 32 | 12 | 19 | 8 | 5 | 7 | 14 |

In the hospital based study out of 319 patients enrolled in the study based on clinical criteria, 267 were confirmed as suffering from extra-Pulmonary TB and included in the study. The maximum number was in lymph nodal group (127) followed by extremity bone and joint (63), spine (38), skin and soft tissues (25), Abdomen (19) (Table 1).

Two patients included in the study based on CTAbdomen findings of intestinal ileocaecal tuberculosis turned out to be Crohn's disease after exploration of intestinal obstruction, resection of ileal segment and HPE (Figure 1).

Figure 1: Crohn's presenting as ileocaecal koch's



Of 11 patients of tuberculous mastitis one of them had positive AFB on microscopy and was started on ATT but as there was no response even after 1 month. Excision biopsy of large multicystic loculated mass discharging serous fluid revealed infiltrating duct cell carcinoma (Figure 2). Two others had chronic non-specific inflammation.

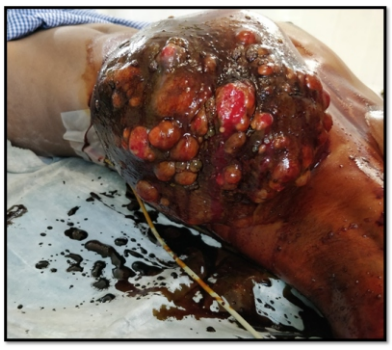


Figure 2: Carcinoma Breast mimicking Tuberculous Mastitis

Chances of misdiagnosing TB on clinical and radiological features is significantly more in abdominal TB compared to other sites, however the difference was not statistically significant between other sites.

Majority of lymph nodal TB patients were diagnosed based on cytological findings (76/127-60%) and extremity bone and joint TB by imaging while other sites it was by HPE of biopsy specimen. Use of FNAC in diagnosing lymph nodal TB being significantly better than in diagnosing TB at other sites.

Overall, CBNAAT was significantly better at detecting extra pulmonary TB compared to cytology (p=0.01), AFB on microscopy and AFB Culture (p= 0.008) while AFB on microscopy was found to be significantly inferior in detecting the disease when compared to all other methods including imaging, cytology and AFB culture.

Of all the minimally invasive methods used for confirming lymph nodal TB, cytology and CBNAAT were significantly better at confirming disease when compared to AFB on microscopy and AFB

culture of pus; difference between cytology and CBNAAT not being statistically significant. In case of Spinal TB, CBNAAT was significantly better than cytology and AFB on microscopy in confirming disease.

Similarly in other skeletal and joint TB imaging features were confirmatory significantly than cytological findings and detecting AFB on microscopy; positive CBNAAT significantly better than cytology and AFB microscopy.

Effectiveness of CBNAAT was in confirming abdominal and skin and soft tissue TB without the need for obtaining tissue for HPE where it was significantly better than cytology and AFB on microscopy.

**Table 2: Sex Ratio**

| SYSTEM AFFECTED | MALES | FEMALES |
|---|---|---|
| LYMPH NODES | 43 | 84 |
| ABDOMEN | 5 | 14 |
| SKIN AND SOFT TISSUES | 4 | 16 |
| BONE AND JOINT | 24 | 39 |
| SPINE | 16 | 22 |

Comparing the distribution of males and females in each group, we saw a pattern of female preponderance to be present with no statistically significant difference between the groups (Table 2).

**Table 3**

| Primary site involved | Number | Previous H/o of TB | BCG immunization | DM | CXR involvement |
|---|---|---|---|---|---|
| Lymph Nodes | 127 | 14 | 93 | 8 | 2 |
| Spine | 38 | 6 | 22 | 9 | 5 |
| Bone & Joints | 63 | 7 | 40 | 5 | 1 |
| Abdomen | 19 | 8 | 9 | 0 | 3 |
| Skin & Soft tissues | 20 | 2 | 15 | 3 | 0 |

Significantly more numbers of patients with abdominal TB gave previous H/o treatment with ATT (8/19) for TB of various sites including meninges as compajred to other groups (Table 3).

Significantly more number of patient's in lymph nodal group were immunized with BCG vaccine in their childhood (93/127) as compared to patients with Pott's spine (22/38), extremities bone and joint TB(40/63) and abdominal Koch's (9/19).

Maximum number of diabetic patients were in the spine group (9) which was statistically significant when compared to patients in other groups.

Evidence of Pulmonary T.B was found in very few patients- only 11 out of 267- majority of that in patients with pott's spine (5/38) and abdominal koch's (3/19) which was significantly more than in TB of other sites.

**Table 4: Need for Surgical Intervention**

| SITE INVOLVED | NEED FOR SURGICAL INTERVENTION | | | NO. OF PATIENTS NOT REQUIRING SURGICAL INTERVEaNTION |
|---|---|---|---|---|
| | DIAGNOSTIC | THERAPEUTIC | TOTAL | |
| LYMPH NODES | 51 | 6 | 57 | 70 |
| SKIN AND SOFT TISSUES | 17 | 1 | 18 | 2 |
| ABDOMEN | 14 | 3 | 17 | 2 |
| SPINE | 18 | 9 | 27 | 11 |
| EXTREMITY BONE AND JOINT | 19 | 2 | 21 | 42 |

There was statistically significant increased need for surgical procedure for diagnosis of skin and soft tissue and abdominal TB than in TB affecting other sites in the study. Pott's spine and Abdominal koch's (Figure 3) needed more surgical intervention for therapeutic benefit which was statistically significant when compared to lymph nodal and other bone and joint disease (Table 4).

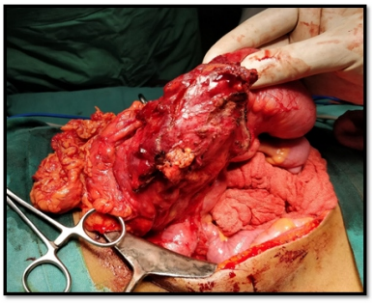


**Figure 3: Ileocaecal Koch's presenting with Acute Intestinal Obstruction**

**Table 5: Healing Time**

| SITE INVOLVED WITH DISEASE | TIME TAKEN FOR COMPLETE RESOLUTION OF SYMPTOMS AFTER STARTING ATT | | NO. OF PATIENTS REQUIRING SURGICAL THERAPEUTIC INTERVENTION |
|---|---|---|---|
| | LESS THAN 6 MONTHS | MORE THAN 6 MONTHS | |
| LYMPH NODES | 121 | 6 | 6 (out of 6) |
| SKIN AND SOFT TISSUES | 17 | 3 | 1(out of 3) |
| ABDOMEN | 12 | 7 | 3(out of 12) |
| SPINE | 2 | 36 | 9 (2 out of 2 and 7 out of 36) |
| OTHER JOINTS AND BONE DISEASE | 5 | 58 | 2(out of 58) |

Table 5 showing spine, bone and joint TB taking significantly longer time to heal compared to other groups irrespective of surgical intervention or duration of ATT.

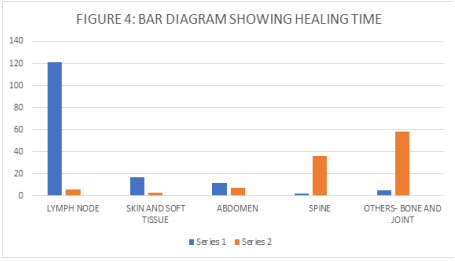



**FIGURE 4: SERIES 1: HEALING TIME <6 MONTHS SERIES 2: HEALING TIME >6 MONTHS**

**Table 6: Community Health Centre Data**

| | COMMUNITY HEALTH CENTRE (CHC) 1 | COMMUNITY HEALTH CENTRE (CHC) 2 |
|---|---|---|

| | TOTAL | AFB+ | RELAPSE | TOTAL | AFB+ | RELAPSE |
|---|---|---|---|---|---|---|
| PULMONARY | 378 | 277 | 86 | 398 | 270 | 90 |
| EPTB | 252 | 0 | 28 | 266 | 8 | 30 |
| TOTAL | 630 | 277 | 114 | 664 | 278 | 120 |

While in none of the patients with extra pulmonary TB, sputum was positive for AFB in CHC 1 and detected in only 8 patients with EPTB in CHC 2 (Table 6) 176 patients (86 in CHC1 and 90 in CHC 2) with pulmonary TB(22.6%) had history of being treated for TB either partially or completely in the part while the relapse rate was 11.2% in the patient's with newly diagnosed EPTB (28/252 in CHC 1 and 30/266 in CHC 2). The difference being statistically significant individually and combined for both CHC's (p value 0.006 and 0.0002 respectively). Only 3 patients were found to be retroviral positive - 2 with pulmonary and 1 with EPTB.

**Discussion:**

It has been known for a long time that tuberculosis is a disease of the immune system with most of the morbidity associated with the infection. Resulting from an exaggerated cell mediated immune response or hypersensitivity reaction forming granulomas with necrotic centres coalescing into an abscess which drains into bronchus in the lung or eats away the surrounding tissues in case of EPTB[1,2].

Which part of the body is affected by tuberculosis is determined by the complex interplay of various factors like genetic makeup of host, bacterial genotype, behavioural, clinical and demographic features [13]. Different lineages of M. tuberculosis are strongly associated with specific geographical locations with EuroAmerican isolates strongly associated with pulmonary rather than meningeal disease; drug susceptibility isolates of Indo-Oceanic and East-Asian lineages of Tuberculous bacilli causing higher mortality to meningitis than those infected with Euro-American isolates [14].

Even the immune response to MTB bacillus is dependent on macrophage function- whether be it necrosis in some or multiplication of bacilli within macrophage resulting in dissemination or miliary tuberculosis in others- dictated by host genetics and infective strain of TB [15].

Much has been written about influence of gender on tuberculosis- quite a few of them concentrating exclusively on gender prevalence [16] and concluding that gender itself is a risk factor for EPTB [5,17,18] which defeats the very purpose of scientific study.

But there is evidence to show that gender difference in susceptibility to TB is sex chromosomal related, differential susceptibility to TB related to sex hormones (specifically estradiol) levels [19], dehydroepiandrosterone (DHEA) levels [20]. Vitamin D deficiency states are more in females due to lack of exposure to sunlight [21]. Even in our study, in all the sites there is increased female to male ratio with no statistically significant difference between the groups.

And contrary to the common perception that TB is primarily a disease of the lungs accounting for major percentage of disease load with many studies reporting a EPTB rate ranging from 10-20% [5,10,13,17], figures from the two community health centres (CHC's) catering to the tuberculous patients revealed EPTB case load of 40% which was close to the study conducted in Nepal [7] and Turkey [22] reporting an EPTB prevalence rate of 48.5% and 49.5% respectively. This is almost equal to that of PTB and while none of the patients from CHC 1 with EPTB had positive AFB in sputum, only 8 patients from CHC 2 were AFB positive. Similarly in our hospital based study CXR evidence of pulmonary TB was found only in 11 patients of the 267 confirmed EPTB (4%).

Thus debunking the long established myth that TB means pulmonary disease and EPTB is an extension of PTB which is still being propagated by various studies published in reputed journals. [3,4]

Another myth which is institutionally propagated is that TB is a disease of poor underdeveloped third world countries which is to be eradicated there itself to prevent its spread to western 'developed' countries and extra pulmonary TB is to be found only in severely immunocompromised patients like those with HIV, post transplant patients and those with diabetes mellitus or in immigrants from Asia and Africa to USA or European countries [13]. In our study none of the patients with confirmed EPTB were retro viral positive and 25 were diabetic out of total of 267 patients- the maximum number of patients with pott's spine.

And in patients enrolled with CHC's only one patient with EPTB and two patients with pulmonary TB were HIV positive out of total of 1294 patients. This conclusively proves that you don't need severe immunodeficiency states for reactivation of either PTB or EPTB.

That TB is a disease of immunological system irrespective of geographical area with major influence of sunlight and vitamin D on body immunity was shown to good effect in a meta analytic study conducted by K.E.Nnoaham and A.Clarke [23]. Moreover there is accumulating evidence that vitamin D replete state provides broad protection against a range of bacterial and viral pathogens, differences in ability of humans to produce vitamin D contributing to susceptibility [24] and inhibiting the growth of M. Tuberculosis in macrophages [25].

Serum cortisol/ dehydroepiandrosterone (DHEA) ratio has a bearing on production of interferon gamma (IFN-γ), a type 1 cytokines response, involved in protective immunity against Intra cellular pathogens like M. Tuberculosis: higher DHEA plasma levels or lower cortisol/DHEA ratio resulting in greater production of IFN- γ and better immune response [26].

That brings us to the crux of the matter: Is EPTB an epidemiological disease to be tackled by surveillance, notification, quarantine and free distribution of drugs with emphasis on notification and delivery of antituberculous treatment (ATT) as advocated by WHO [27,28] or does it require specialist care for proper diagnosis, differentiation from other diseases that affect that particular system, follow up and surgical management if necessary?

Critical Revision of literature showed almost all the clinical published studies are either by pulmonologist [9,10,18,22,28], epidemiologists [3,5,9,10,13,16,20] or from departments of clinical infectious diseases /microbiologists [3,4,8,17,22] with criteria for inclusion in the studies ranging from isolating AFB from tissues with positive AFB cultures to basing the diagnosis on strong clinical evidence by 4 medical officers [28]. This, when compared to evidence from present study, showing AFB on microscopy and positive AFB culture being significantly inferior to FNAC and CBNAAT in diagnosing EPTB and chances of misdiagnosing TB solely on clinical features being quite high- with abdominal TB significantly more prone for being confused with other pathological conditions based solely on clinical and radiological features; in pott's spine and skeletal TB, CBNAAT and imaging being significantly better than AFB on microscopy on diagnosing disease, prove that those studies may not be based on sound criteria.

Our study has shown that there is no standard method of investigation for diagnosing EPTB originating at various sites except for obtaining tissue for HPE, which is not practicable as feasible in all the cases. So it's left to the physician or surgeon of that speciality to arrive at a diagnosis based on the characteristics of the disease affecting that particular system. This can be reasonably detected by either a non-invasive investigation like imaging (as in for skeletal and spine TB) or a minimally invasive one like FNAC (as for lymph nodal TB). But this requires a competent radiologist and a cyto-pathologist thus making it a multidisciplinary approach for

diagnosing EPTB.

Overall bone, joint and spine TB took significantly longer time to heal ($p<0.001$) compared to other sites but when taken individually patients with cold abscess formation in lymph nodes or spine took longer time to heal (beyond 6 months) even though cultures were sensitive to INH and Rifampicin.

Similarly in patients with skin and soft tissue TB, excision of single sinus was curative (Figure 5) while multiple sinuses took 2-3 months more even after completion of ATT for complete resolution. In patients with pott's spine all the patients requiring therapeutic surgical intervention (9) were already on ATT, having symptomatic improvement in neurological function after drainage of abscess, removal of diseased bone and cord decompression; cultures done in some of them showing sensitivity to INH and Rifampicin.

**Figure 5: Tuberculous Sinus completely healed after excision even before 1 month of ATT.**

These observations bring into focus the over dependence on ATT, the stress on various treatment regimens sometimes extending upto 2 years (instead of usual 6 months), threat of multidrug resistance (MDR) and extended spectrum MDR. Fallibility of pharmacotherapy for tuberculosis- both pulmonary and extrapulmonary type- has been shown in a recent in vitro study where induction or stimulation of macrophage function has shown eradication of M Tuberculosis bacteria from various tissues like lung, liver, spleen and kidney at reduced doses- even less than one tenth of Rifampicin [29]. This only strengthens the age old wisdom gleaned over years- faced by a patient who has lost his power to heal, the most famous surgeons are reduced to impotence [30].

So the way forward is comparative study of patients with cold abscess- anywhere in the body- between those put on ATT and in whom ATT is discontinued following surgical intervention to know if ATT is of any benefit in patients with cold abscess formation. Other studies could focus on ways of moderating the immune response and role of immunomodulators similar to those used in Crohn's disease, in patients with EPTB who don't have features of military TB.

And in patients with recurrent disease even after completion of course of ATT, affectivity of vitamin D therapy may be tested compared to placebos instead of repeating the ATT course.

## CONCLUSION:

There is no uniform or fixed method of diagnosing EPTB. It varies according to system/site involved- FNAC for LN TB, HPE for skin, soft tissue and abdominal TB, MRI and HPE for pott's spine and imaging for skeletal, bone and joint TB.

EPTB is not related to pulmonary TB, probably caused by reactivation of long dormant bacilli lodged in that tissue and not due to spread from pulmonary TB- the exact cause for reactivation is that particular site still unknown but may be surmised to be multifactorial with virulence of tubercle bacilli, presence of myelolymphoid tissue, immune system reactivation and hormonal factors playing major role; lymph nodal TB (most common form of EPTB) occurring relatively more in patients with better immune system, abdominal and spinal TB in patients with decreased immune function. Detection of AFB on microscopy and culture of pus for tubercle bacilli of very limited value with false positives causing delay in correct diagnosis in turn resulting in mismanagement with deleterious effects. CBNAAT even though of better sensitivity is still riddled with high costs- both economically and due to false positivity.

Surgical intervention is of significant diagnostic benefit in all forms of EPTB and therapeutically beneficial in spine TB.
Time to heal depends on the site involved with the disease immune function specifically macrophage activity of that particular tissue and not on the duration of antituberculous treatment.

Further research should concentrate on ways of boosting the innate immunity either by vaccine or any other method of inducing macrophage function than on trying to eradicate mycobacteria.

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