Review Article

Challenges in Diagnosis of Extrapulmonary Tuberculosis

Jyotirmoy Pal[1], Moni Sankar Bhattacharjee[2]

Even in the era of twenty-first century tuberculosis is still considered as a major health burden around the globe particularly around the Indian sub-continent. Though Pulmonary system is the principal site for Mycobacterium but extra-pulmonary involvement is not so common. Extra-pulmonary involvement can be seen in isolation or even with pulmonary involvement also. Immunocompromised individuals like HIV-affected individuals carries a greater risk for disseminated tuberculosis with involvement of multiple extra-pulmonary sites but Immunocompetent persons also can develop extra-pulmonary manifestation. Among all sites, Lymph nodes are the commonest in extra-pulmonary involvement.

Though conventional Sputum smear examination and culture sensitivity is still reliable in diagnosis of pulmonary tuberculosis but are less helpful in extra-pulmonary cases due to its paucibacillary nature. Modern molecular methods in background of strong clinical suspicion with or without radiological evidences forms the pathway to confirm the diagnosis. These Diagnostic difficulty makes the delay in response to treatment in these patients.

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Key words **: Tuberculosis, Immunocompromised, Disseminated, Lymph nodes, Paucibacillary, Molecular method.**

Tuberculosis is the one of the major health problems in India from ancient times and it covers almost one-fourth of total burden of tuberculosis of the world. RNTCP program and DOTS initiative have decreased the incidence of pulmonary tuberculosis where diagnosis is based on demonstration of Mycobacterium by microbiological, cytological or by histopathological way but not so in case of Extra Pulmonary Tuberculosis (EPTB) where conventional smear and culture have less yielding value.

Extrapulmonary tuberculosis means involvement of any organ other than Lungs.

However, **More common site : Lymph node**

Less common site : Breast

Pleura	Pericardium
Bone	Pancreas
GI tract	Eyes
CNS	
Genitourinary	

Prevalence of Extra-pulmonary tuberculosis is almost **15-20%** in **immunocompetent** persons but **more than 50%** in **immunocompromised** individuals like in HIV positive individuals[1]. In the context of **HIV and tuberculosis** both presentations,**disseminated tuberculosis like TB lymphadenitis, pleural effusion and TB meningitis are common** where Classical sputum examination shows low positivity with atypical body fluid chemistry that makes **CBNAAT testing mandatory** for allcases.

Editor's Comment :

- Extrapulmonary Tuberculosis can occur both in immunocompetent and immunocompromised individuals.
- Diverse clinical features with absence of definitive diagnostic modality makes the difficulty.
- Clinical findings are the main clue to diagnosis which must be corroborated with investigative findings.

CHARACTERISTICS OF EXTRAPULMONARY TUBERCULOSIS :

Extrapulmonary Tuberculosis is —

- **Pauci-bacillary** in nature
- **Lesser contagious and highly disseminated**
- Radiology suggestive but not diagnostic in many cases.

Along with accessibility challenges in many cases with less predictive value of classical diagnostic modalities makes the diagnosis of extra-pulmonary tuberculosis difficult and often missed.

CHALLENGES IN EXTRAPULMONARY TUBERCULOSIS :

Definitive diagnosis of pulmonary tuberculosis done by demonstration of Mycobacterium directly in sputum smear examination or by culture.

Contrary to that in extra pulmonary tuberculosis,

Department of Internal Medicine, RG Kar Medical College and Hospital, Kolkata 700004
[1]MD, FRCP, FICP, FACP, WHO Fellow, Professor
[2]MBBS, Junior Resident and Corresponding Author

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as it is pauci-bacillary in nature **sensitivity of smear examination is low (<50%), culture takes long time to provide results** definitive diagnosis of extra-pulmonary tuberculosis remains a great challenge to our physician.

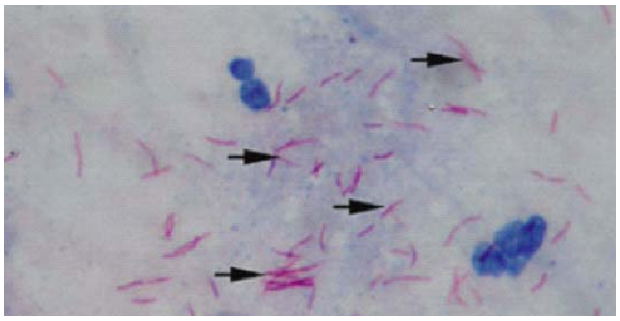
SENSITIVITY OF CULTURE OF SPUTUM IN VARIOUS EXTRAPULMONARY CASES :

ABDOMINAL TB	-	28-50%
TB PERICARDITIS	-	10-11%
TB MENINGITIS	-	24-29%
TB LYMPHADENTITIS	-	5-14%

DIFFERENT DIAGNOSTIC MODALITIES :

I. FINE NEEDLE ASPIRATION BIOPSY AND HPE :

Epithelioid cell granuloma with caseous necrosis is highly suggestive of presence of tubercular bacilli. However, in immunocompromised patients, **suppuration is found instead of caseation**. Z-N staining is helpful for detection but due to **paucibacillary nature sensitivity of AFB in microscope less than 50%.** Sensitivity and specificity can be increased up to 80% with modern fluorescent microscopy and PCR technology. Excision biopsy also can be done with increased sensitivity where Fine needle aspiration is inconclusive.



SMALL RODS, SLIGHTLY CURVED OR STRAIGHT, GRAM POSITIVE MYCOBACTERIUM TUBERCULOSIS SHOWING ACID FAST STAIN POSITIVITY

This kind of granulomatous presentation also seen in other conditions **like Sarcoidosis, Brucellosis, Non-tubercular mycobacteria and Histoplasmosis** and tubercular bacilli have a chance to be destroyed in formalin solution so the tissue sample must be kept in saline solution.

Challenges : difficulty in access of tissue particularly from deeper part of Body like Retroperitoneal Lymph Nodes , Mediastinal Lymph nodes etc.

II. CULTURE :

Isolation of mycobacteria from clinical specimen by **culture is the gold standard for diagnosis of extra-pulmonary tuberculosis**[2]**.**

Advantages are —

- More sensitive method as it requires only 100 bacilli
- Species detection and drug sensitivity assessment can be done in same settings.

Limitations are —

- Yield can vary from **30-80%** as they are paucibacillary in nature.
- Culture in solid media takes more time (2-6 weeks) though culture in liquid media takes less time (7-14 days).

III. ANALYSIS OF BODY FLUID :

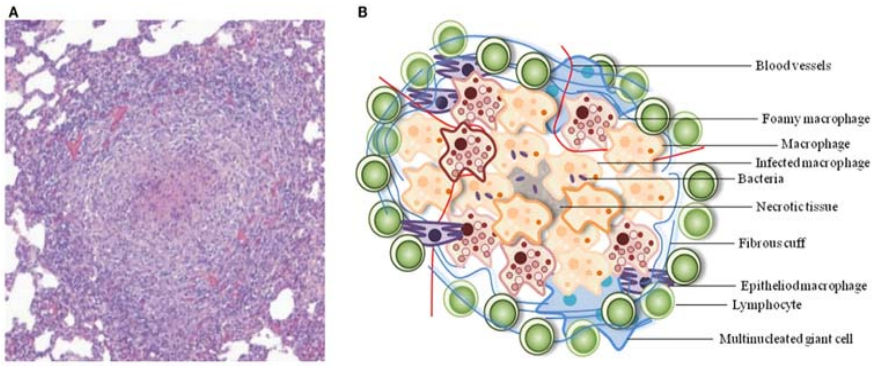
Mainly Pleural, Pericardial, Peritoneal, Synovial and Cerebrospinal fluid analysis has been done:

(a) CHEMISTRY:

- Usually,these body fluids are **Exudative** in nature with **lymphocytic predominance** in extrapulmonary tuberculosis but neutrophilic leukocytosis found in early phase of TB meningitis and tubercular pericardial effusion.
- **Cobweb formation seen in CSF** of Tb meningitis cases and atypical body fluid chemistry noted in immunocompromised patients.
- More than 5% mesothelial cells in these fluids exclude tuberculosis

(b) ADENOSINE DEAMINASE LEVEL: (ADA)

- This enzyme found in all human tissue particularly in T-lymphocytes of lymphoid tissue where it converts adenosine to inosine.
- Excessive stimulation of T-lymphocytes by mycobacterial antigen causes release of ADA
- **High ADA level is not specific** to tuberculosis, it can be elevated in lymphoma, rheumatoid arthritis, empyema and parapneumonic effusion also



• **Estimation of Isoenzyme may be helpful in doubtful cases. ADA2 is more elevated in Tubercular pleural effusion than other causes. ADA1 more in parapneumonic Pleural effusion.**

ADA	Cut Off	Sensitivity	Specificity
Pleural Effusion	40 IU/L	92%	89%
CSF	10 IU/L	79%	86%
Cirrhosis	27IU/L	100%	97%
Pericarditis	40 IU/L	88%	83%

IV. MOLECULAR METHOD :

Highly Sensitive (can detect even 10 mycobacterium) and specific method and helps in rapid diagnosis also[3].

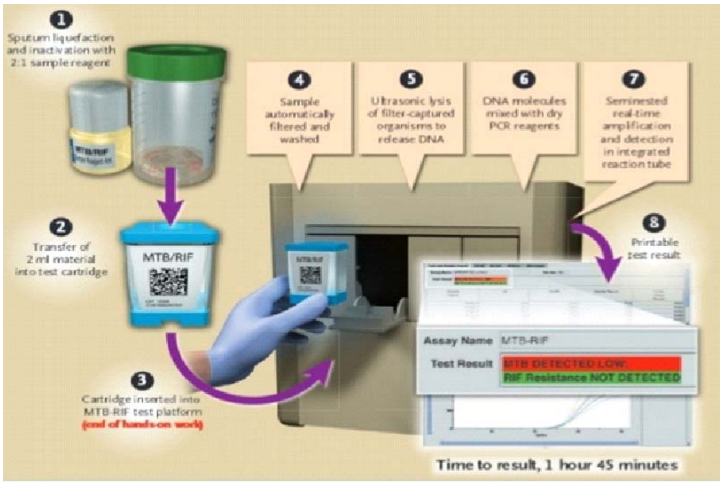
(a) PCR Technology :

• Useful in various clinical samples.

• Can detect **MPB64** or insertion sequence **IS6110**

• Highly sensitive but false positivity makes limitation of this method

(b) CBNAAT :



CBNAAT SEQUENCING :

• Automated cartridge based nucleic acid amplification test

• Result obtained **by 2 hours**

• Can detect mycobacterium in both body fluids and tissue samples

• Can detect Rifampicin resistance also

• Sensitivity varies according to sample like in

Lymph node — 83.1%
CSF — 80.5%
Pleural Effusion — 46.4%

• CBNAAT using pleural tissue more sensitive that pleural effusion

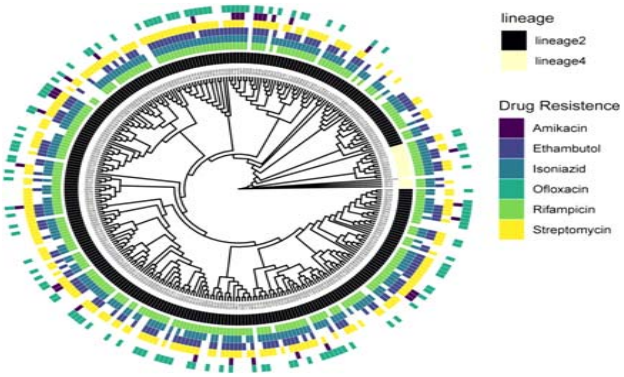
• Overall sensitivity**- 83.1%** and specificity- **98.7%**

(c) LINE PROBE ASSAY :

• Initially approved for sputum positive cases only but now used in sputum positive, sputum negative and extra-pulmonary tuberculosis cases (culture positive should be).

• Rapidly molecular testing for detection of MDR pathogen from pulmonary specimen

• Can detect Mycobacterium with **INH resistance** (inhA, KatG gene) and **rifampicin resistance** (rpoB gene)



V. IMMUNOLOGICAL TESTING METHOD :

These have limited diagnostic value, only used to support diagnosis of extra-pulmonary tuberculosis.

(1) TUBERCULIN SKIN TEST (TST) :

• Can be false positive and negative

• **POSITIVE test -** Active TB, Past infection, BCG vaccination, Sensitization to mycobacterium antigen

• **NEGATIVE test -** Immunocompromised and undernourished patients.

• **CANNOT DIFFERENTIATE BETWEEN PRESENT AND PAST.**

(2) INTERFERON GAMMA RELEASING ASSAY (IGRA) :

• Measurement of INF-gamma by activated mononuclear cells response to different tubercular antigen

• Available as **Quanti FERON TB GOLD** and **TB SPOT.**

• **QuantiFERON TB GOLD** - Sensitivity— 72%
Specificity—82%

• **TB SPOT**— Sensitivity-90%
Specificity-68%

• Sensitivity higher in chronic infection rather than acute infection

• Body fluid is more sensitive than blood in diagnosis.

- IGRA positivity indicate Tubercular infection of Body, not disease. Helpful to detect Latent infection. But in India there is very high prevalence of Latent TB infection , that is why in India IGRA not recommended.

VI. ANTIGEN DETECTION :

- Antigen 5, 14kDa, antigen a60 and LAM
- These antigens lack sensitivity and specificity
- Limited value
- And not used in India

VII. IMAGING: (LIKE USG, CT scan, MRI and PET Scan)

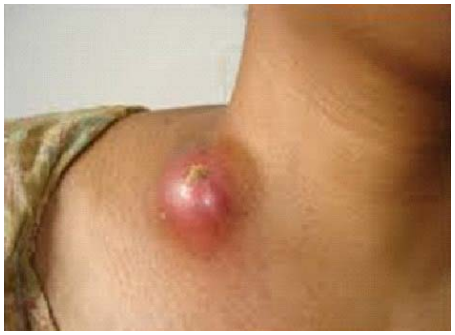
- Not diagnostic but suggestive
- Can help in getting tissue for HPE

DESCRIPTION OF VARIOUS EXTRA-PULMONARY TUBERCULOSIS :

A. TB Lymphadenitis :

Most frequent complication of extra-pulmonary tuberculosis in Indian sub-continent.

- 35% among extra-pulmonary tuberculosis and 60% among HIV-TB cases.
- **Cervical, mediastinal and abdominal lymph nodes** are commonly affected.
- **Cold abscess and sinus formation are common** though can present with obstructive features sometimes.
- Diagnosis mostly depends **on FNAC** derived sample tissue histopathology examination and **Z-N staining** for detection of acid-fast bacilli.
- **Excision Biopsy** recommended where FNAC could not derived enough sample for histopathology.
- Incision biopsy is not recommended as it may create sinus formation.
- As per RNTCP guidelines**, gene X-pert technique is recommended in each sample.**

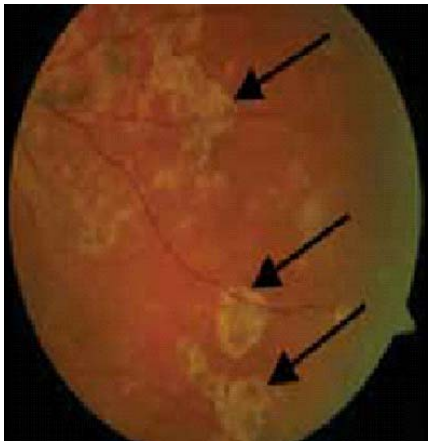


Inflamed, swollen, soft and fluctuant Cervical Lymph Node leading to Abscess formation

B. Tuberculosis of Eye :

Posterior uveitis is common form of ocular TB. Granuloma formation seen in choroid, iris and ciliary body. There are some challenges present here like-

- Constitutional symptoms are often absent.
- It is difficult to get microbiological evidence
- That makes presumptive diagnosis is only choice.



C. Renal Tuberculosis :

- Often starts insidiously with nonspecific symptoms.
- Persistent painless pyuria with negative urine culture.
- Detection of mycobacterium is the key to diagnosis but AFB staining is not reliable due to presence of another acid-fast bacilli Mycobacterium smegmatis.

D. Urinary Tract TB :

- Smear and culture sensitivity from urine sample low.
- In immunocompromised patient sensitivity increases.
- Lipoarabinomannan (LAM) increases yield of renal TB.

E. CNS Tuberculosis :

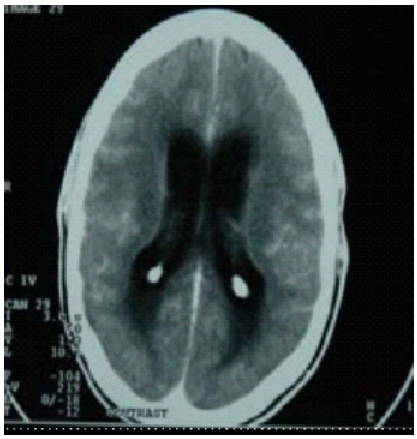
- Usually presented as **meningitis or space-occupying lesions.**
- **CSF culture is the gold standard** for diagnosis of TB meningitis however laboratory data lacks sensitivity as culture is positive only in 25-70% cases.
- **CSF ADA** Value **more than 8 IU/L** have **sensitivity of 96%** but **low specificity of 59%** only as it can not differentiate between TB meningitis and pyogenic meningitis[4].
- **Gene X-pert now considered as first line** due to rapid results (obtained within 2 hour) and high sensitivity (100%), specificity (60%).
- IGRA have moderate accuracy in diagnosis.
- Among neuro imaging-

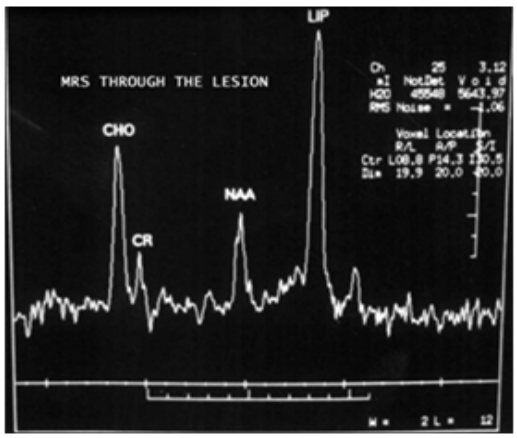
CT Scan/ MRI Brain shows tuberculoma, basal exudates, hydrocephalus.

MRI Spectroscopy helps in detection of tuberculoma due to **high lipid lactate peak.**

F. Abdominal Tuberculosis :

- Usually have **florid presentation like Ascites, hepatosplenomegaly, Intestinal obstruction, doughy abdomen, hepatic abscess**.
- Diagnosis is done by same way like demonstration of Acid-fast bacilli, culture shows growth of mycobacterium.
- **But due to paucibacillary in nature and**



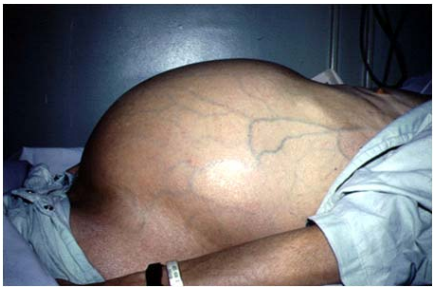


absence of easy accessibility of tissue, it is often difficult to diagnosis.

- Ascitic fluid study shows **exudative fluid with high ADA level.ADA morethan 39 IU/L suggestive but false-positive results** may be seen in other inflammatory condition and false-negative results may be seen in immunocompromised patients.**PCR have low sensitivity and Gene X-pert also have limited value as yield is low.**
- Mantoux test, chest X-ray, IGRA, High ALP level are suggestive.
- **Abdominal radio-imaging also suggestive but not diagnostic**.
- Sometimes endoscopy may be helpful in obtaining tissue for histopathology.

G. Tubercular Pleural Effusion :

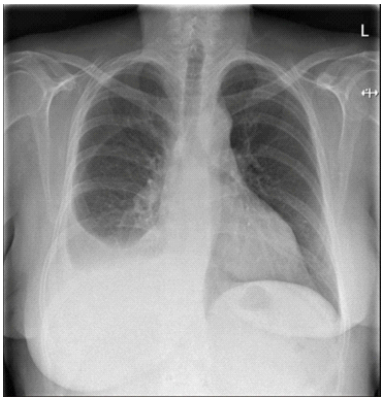
- Usually **Right sided,** bi-lateral rarely
- Can present as Acute, subacute or chronic illness
- Instead 0f fever, chest pain and non-productive cough are common.
- **Pleural fluid study is the mainstay of diagnosis.**
- Pleural fluid Aspiration shows neutrophilic predominance in early stages followed by lymphocytic dominance. **High ADA value suggestive of tuberculosis, but false positive results** found in lymphoma, empyema and late para-pneumonic pleural effusion also.
- **Pleural fluid CBNAAT** have **sensitivity of 45%** but specificity 99%
- Pleural effusion is **pauci-bacillary in nature**, have smear positivity of 5% only with culture positivity of 20-30%. **Culture positivity increases if biopsy included.**



- Pleural biopsy has been done only in **high suspicious cases.** Thoracoscopy or USG guided biopsy have higher yielding value.
- Sputum may be positive in 23% (induced sputum) and culture in 52%
- **IN TUBERCULAR PLEURAL EFFUSION NO TEST IS DIAGNOSTIC.**

CONCLUSION :

- Diverse pathogenesis responsible for diverse clinical and pathological diversity.
- No single test is adequate.
- Which makes diagnosis of extra-pulmonary tuberculosis challenging
- High index suspicion is required and test results must be corroborated with pathological results.
- Another challenge is DOTs therapy based on Sputum positivity . In Extrapulmonary Tuberculosis yield of getting Sputum is very Low. So tissue diagnosis is very crucial in initiating treatment , as scope of empirical therapy have narrowed down in recent national tuberculosis guideline.



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